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BCG Vaccination in Venezuela*

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In Venezuela tuberculosis represents the prime cause of death. If the exact data of 30 cities were compiled, which total about 900,000 inhabitants, representative of nearly 25 per cent of the country's population, a crude coefficient of mortality of 268 per 100,000 inhabitants is obtained, with ample variations. In Caracas and Maracaibo, the said coefficient reaches 152 and 178 respectively, showing a marked tendency toward decrease. At the beginning of the century it was estimated at around 600 in the former city. Tuberculosis represents 15 per cent of all causes of death.

The great territorial extension and form of distribution of the population concentrated along the Caribbean coast on the North and the range of the Andes mountains in the West, explain many of the features of our epidemiology with regard to tuberculosis since 66 per cent of the Venezuelan population is dispersed in many small urban centers and rural zones, a large portion of the country being almost uninhabited. The studies on infection with the tuberculin test particularly show marked differences, greatly surprising at times, but in urban centers the prevalence of massive infection is found, the lowest index, 20 per cent positive, being among children of poor living conditions from 0 to four years of age. In children up to 14 years of age, in cities, the rate of infection rises to above 50 per cent. In adults beyond 14 years, the rate is more than 80 per cent. On the other hand, in some rural zones, the rate of infection is much lower and slower, showing only 50 per cent reactors in the middle-age group; though some rural zones are found with a high rate of infection.

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These reasons, our low standard of living and a campaign which though intensely developed, is still too young for the proper control of the illness, particularly there still being a lack of beds, explains the interest which has always been shown in Venezuela with regard to the BCG vaccination problem. Introduced by the Department of Health in 1932, it was first applied in Caracas in March 1933. The strain of BCG was received from the Pasteur Institute. The technique employed for its conservation and the vaccine preparation is that recommended by Calmette-Guérin at that time. The vaccines are tested for virulence by subcutaneous and intraperitoneal guinea pig inoculations.

At present two cycles are made for the conservation of the virulence of the strain: the first, lasts eight months during which time the cultural passages are made only on pepton broth, 5 per cent glycerinated, and the second, of two months duration, with passages on bile-potato medium. The passages are made every 15 days. To prepare the vaccine the Sauton medium is used in accordance with instructions of the Pasteur Institute. Transfers are made every seven days and the culture used from 12 to 14 days. The nephelometric method is used for dosage concentration.

From 1933 to 1938 oral vaccination was used, the dosage being 3 centigrams administered in three doses at one day intervals. Since 1938 the intracutaneous injection has been used (0.15 milligram). The vaccine must be administered within 10 days of its preparation. Almost 100 per cent of children vaccinated became tuberculin reactors, tested with intracutaneous injection eight weeks after the intracutaneous administration. Sensivity decreased in the following months. When negative, revaccination is effected.

Since Calmette's first publications, a sufficient number of work observations have been made, especially with regard to experiments on animals, to allow a favorable attitude toward the method, yet on the other hand, nothing has been so difficult as the demonstration of the protective value of the vaccine in human beings so as to convince and conquer the prudent attitude of a responsible Health Administration.

It is easily understood that in an illness, such as tuberculosis, so directly influenced by conditions of environment, economics, habits and education, and in which the experiences require a sufficient number of years, it would be difficult to find the vaccinated group and the control group which permit adequate comparison of complex conditions that exercise an indirect action of non-specific character over the vaccinated group, especially one of long experience and duly studied. To maintain these conditions of environment which exercise an action on the nutritional state and therefore on the resistance to the illness, without allow-

ing the educational factor of the vaccinated group to influence the conditions of exposure to contagion, thus falsifying the results within a method with which one cannot aspire to obtain but a relative increase of the resistance, has been the difficulty to overcome. On the other hand, the statistical value of experiences with small groups which better fulfill the requisites, are less decisive.

Venezuelan experience which dates from 1933 and consists of over 30,000 vaccinations, has been considered inadequate by the Department of Health to resolve the question of the protective value of the method. In the Reports of the Second Venezuelan Tuberculosis Congress held in Maracaibo in 1943 and in the Sixth Congress of the ULAST in Havana, 1944, we stated that the conditions of the medium and the possibilities of a recently created antituberculosis army, the vaccinated group, duly studied, has always been considered a selected group. For statistical comparison, it has enjoyed advantages over the control groups due to the existence of a special Dispensary with personnel for applying the vaccine and controlling those vaccinated, the additional services of Puericulture and Pediatrics and the fact that the control of many cases is lost due to the frequent migration of the population vaccinated in maternity centers. These circumstances result in that those vaccinated and fulfilling during a sufficient number of years all the requisites for a correct observation of the cases, evidently constitute the better group.

We have tried to avoid committing the frequent statistical error of comparing the general mortality of the vaccinated with that of the corresponding infant population, since of those vaccinated, the prematures and all cases of congenital debility have already been eliminated.

We have been unable to realize as complete experiments as has been done in other countries, because all our efforts during these years have been concentrated on organizing the ordinary epidemiological methods for tuberculosis control with insufficient auxiliary personnel.

We have preferred a position of strict criticism until such time as the investigations presented fulfill the necessary scientific requirements, feeling that no advance can be made in the solution of the problem until this has been achieved. Proof of this is the lack of proportion between the thousands of existing publications and those which are actually utilized for establishing judgments on interesting questions which may arise. Authors on cumulative works on the matter are also in accord with this point of view.

It is curious to note the lack of statistical perfection where a subject so complex as a *preventive* method for tuberculosis is

concerned, as compared to that used for establishing the value of a new therapeutic method.

We consider that the reasons for often adopting an insufficiently critical attitude in the problem of the BCG vaccine, are principally the following:

First: The enormous disproportion in the majority of the countries, between the tuberculosis problem and the insufficiency of means for attacking it, a situation which frequently creates a sentimental attitude; and

Second: More rational and of greater scientific character, is the solidly experimental basis of the method established by Calmette himself, and his collaborators which favored the application of the method to human beings. It is this firmly established scientific basis which has permitted overcoming all the vicissitudes until arriving at this present stage, but this is no reason for omitting the indispensable requisites when studies of evaluation for application to Public Health are presented.

As stated above and because of the accepted fact that the BCG vaccine is harmless, possessing a certain immunizing action, this has been held in Venezuela as a complementary prophylactic method, without the means for tuberculosis control by the proved epidemiological methods, having suffered in the least. This explains the slow and gradual development in its field of application, still limited to 12 Maternity Centers in the country, and where conditions permit its use in the new-born if their parents so desire, prematures being excluded.

During the past two years in Caracas, school children have been vaccinated, also optional, who have reacted negatively to the tuberculin test. A limited trial application has also been made on tuberculin negative infants between 0 and two years in Infant Care Clinics. Besides the negative test with ten milligrams of old tuberculin, the complementary requirement needed for the anergic children is a fluorophotograph of 70 millimeters with normal result.

As may be seen no definite change in the Sanitary policy in this respect has developed in the past 15 years. Besides the reasons just mentioned, this attitude has been influenced by the fact of the recent Sanitary organization of the country, for which great efforts were necessary to obtain the proper state of mind that would permit real progress in the antituberculosis campaign, the first programs of which are being developed by means of the classical epidemiological measures. The success of these programs must not be compromised with other solutions not clearly defined. For example, this year Venezuela will have 1,000 beds more in the Tuberculosis Division with an adequate organization, and an

officially accepted program, already under way, provides that within 10 years the country will have the required number of beds as provided for in our campaign.

Confronting special technical difficulties for the correct application of the National Program of BCG Vaccination, we have concentrated our efforts towards the realization of the primary measures, such as: extensive epidemiological studies, enlargement of the Central Laboratory for preparation of the vaccine, increase in personnel and creation of a laboratory for preparation of tuberculin. But it is to be desired that before placing in operation, certain indispensable questions on the sanitary administration be resolved, because of the diversity of opinions, such as the elaboration and different strengths of the vaccine, its application, the duration of the immunity period and manner of appreciating same, periods for revaccination, and naturally not taking into consideration the methods for evaluating results.

SUMMARY

Therefore, the Venezuelan Sub-Committee which studied the subject of prophylaxis of infantile tuberculosis at the Ninth Pan-American Pediatric Congress, held in Caracas in January of last year, enthusiastically seconded the recommendation formulated by the said Congress on the necessity of constituting an International Committee of Bacteriologists, of Physicians and of Statisticians, to study the manner of unifying the procedures of elaboration, application and evaluation of results obtained with the BCG vaccine, a step which would effectively assist its application on a sanitary scale in countries, such as ours.

RESUMEN

El subcomité venezolano para el estudio del BCG que estudió el asunto de la profilaxis de la tuberculosis infantil, en el 9o. Congreso Panamericano de Pediatría, que tuvo lugar en Caracas en Enero del último año, secundó entusiastamente la recomendación formulada por el Congreso sobre la necesidad de constituir un Comité Internacional de bacteriólogos, médicos y técnicos de Estadística, para estudiar la manera de unificar los procedimientos de elaboración, aplicación y valuación de resultados obtenidos con el BCG, un paso que seguramente ayudará efectivamente en la aplicación de la misma en una brigada sanitaria en países como el nuestro.

Concurrent BCG Vaccination*

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1) The name "Concurrent BCG Vaccination" has been adopted to express the type of tuberculosis immunization to be given to children permanently exposed to tuberculosis since birth. This terminology was chosen because the period of time of this immunization "concurrs" with virulent contact during the period when the human body is greatly susceptible to tuberculosis.

Such a vaccination is not in accordance with Calmette's recommendation as to avoid any virulent contact of the vaccinated individual during the six to eight weeks following the BCG examination. In Brazil, where there is yet a lack of medical and socio-economic resources to secure the isolation of children of tuberculous families, the use of this method of vaccination was justifiable.

Concurrent BCG Vaccination is given orally in doses varying from 90 to 100 milligrams during the first days of life, and followed by oral monthly re-vaccinations with 100 milligrams up to the sixth month.

Peroral BCG vaccination† has been practiced in Rio de Janeiro since 1927 and 222,054 newborn infants have been vaccinated through December 1947. A total of 52,279 children were carefully followed up for an average of three to four years by the Brazilian League for the Control of Tuberculosis.

The work of A. de Carvalho,⁹⁻¹⁴ McDowell Jr.,¹⁷ Guedes-Pereira¹⁶ and others revealed a smaller incidence of tuberculosis among the vaccinated children than among the non-vaccinated.

In 1935 Carvalho⁹⁻¹⁴ vaccinated 7,728 children of different ages, and of these, 267 were exposed to tuberculosis one time or another during childhood, and 128 during lactancy. In spite of the close contact with tuberculosis after vaccination, the tuberculosis mortality among this group in the first year of life was only six deaths (4.68 per cent; 23.4 per cent among non-vaccinated). There are not accurate data available in the country in regard to the tuberculosis mortality of children in their first months of life, and a satisfactory comparison cannot be made between the

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†Subcutaneous and intracutaneous routes were tried and proved less effective than the oral route, when using the special "orovaccine" of Rio.

specific mortalities among vaccinated and non-vaccinated children in Rio de Janeiro.

A) Fialho¹⁵ performed 550 necropsies on children from birth to two years who did not have a diagnosis of tuberculosis and who died in a communicable disease hospital. He found that 14.73 per cent of these necropsied revealed tuberculosis as the cause of death. It must not be forgotten, however, that according to present knowledge the tuberculosis mortality among non-vaccinated children exposed to tuberculosis in the first year of life lies between 10 and 50 per cent. Furthermore, comparing the specific mortality between vaccinated and non-vaccinated children exposed to tuberculous families, a decrease in the number of deaths is observed (Saye,¹⁸ four times smaller; Aldershoff and Van Den Bergh, two to ten times smaller, and Baudoin,⁸ 14 times smaller). Carvalho⁹⁻¹⁴ studied in Rio de Janeiro 48 children who received BCG, and 53 who did not, all of them from tuberculous families. During the first year of life six deaths from tuberculosis occurred in these children; one among the vaccinated group and five among the non-vaccinated.

Analyzing the common methods of preventive immunization used against different infectious diseases (diphtheria, typhoid fever, whooping cough, tetanus, etc.) it is easy to observe that none of them are entirely satisfactory in conferring immunity, when only one isolated antigenic stimulus is given. The same should be considered when using the BCG vaccination.

The well known fact that BCG immunization is comparatively more difficult than that against other diseases, justifies the necessity of repeated doses, one or more times. This should be done in such periods of time as to provide satisfactory supplementary antigenic stimuli, as is the case when using booster inoculations.

Because of all these facts the concurrent BCG vaccination was conceived and used, but only after it was determined that there was a complete innocuity of the BCG cultures in use (20 years), and the perfect tolerance of tuberculin reactor children and adults, to the repeated use of large doses of BCG by mouth.

It seemed that the best and quickest way to evaluate the merits of the concurrent BCG vaccination would be its use among newborns in contact with tuberculosis and then follow up and observe the differences in the specific morbidity and mortality among these children (vaccinated, non-vaccinated, or vaccinated only at birth) during the first years of life.

2) A) *Procedure for the Concurrent BCG Vaccination.*

During the period February 1945 - February 1946, 61 newborn

infants were vaccinated. Of these newborns 34 belonged to families where there was a case with positive sputum (group I), and 27 from families where tuberculosis was under treatment (group II) and the cases generally had direct smear negative for acid fast bacilli.

For both groups the following were taken into consideration: (a) the personal hygiene of the tuberculous person and members of household; (b) the type of home; (c) the financial standards of the families; (d) the past tuberculosis history in the families; (e) the control of other children living with the vaccinated groups; (f) the x-ray examination of all adults in the household.

B) *Method*: The oral route was always used both in the first vaccination and any following re-vaccinations. The vaccine used was of the same type, source, and not older than 10 days and, was prepared from pellicles of 13-14 days, in special liquid medium (A.A. medium) under nephelometric bacilli concentration count (10 mg. of BCG per 1 cc.).

In the first days of life, each child received three doses of 30 milligrams of BCG at two or three day intervals. Children born in maternity hospitals were vaccinated before home contact. At the Clinic Control Service, re-vaccinations were done in doses of 100 milligrams of BCG and generally repeated every month, for a period of six months. Of the total children under observation (61), 32 received a total dose of 590 milligrams, and 29 children received smaller doses because of: (a) the death of source case before six months of life of baby; (b) the isolation of source case in hospital; (c) the failure of family to bring child to clinic for periodic re-vaccinations; (d) uncooperative attitude of families.

TABLE 1: Concurrent BCG vaccination in Groups 1 and 2 according to the total doses of BCG as well as to sex and color of the vaccinated new-born.

BCG DOSES	GROUP 1				GROUP 2				TOTAL
	MALES		FEMALES		MALES		FEMALES		
	White	Colored	White	Colored	White	Colored	White	Colored	
590 mg.	6	4	5	3	9	1	4	0	32
490 mg.	6	0	1	0	0	0	1	0	8
390 mg.	0	0	2	1	3	0	2	0	8
290 mg.	1	0	0	2	3	1	1	2	10
190 mg.	1	0	1	1	0	0	0	0	3
	14	4	9	7	15	2	8	2	61

Table 1 shows the distribution of the two groups studied by sex, color and dose of BCG.

32 children received 590 mg. of BCG
8 children received 490 mg. of BCG
8 children received 390 mg. of BCG
10 children received 290 mg. of BCG
3 children received 190 mg. of BCG

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C) *Follow-up*: The follow-up was carried on a monthly basis for the first six months and thereafter, according to individual need insofar as pediatric care was concerned. In some instances, children under good health and good family conditions were followed by nursing home visits. One child (group II) moved away from Rio as well as from his sick father; nevertheless, information continued to be secured through the family.

The medical control of the children was done by (1) routine pediatric and nutritional care, and (2) special investigation insofar as tuberculosis (primary) was concerned, as for instance: (a) tuberculosis past history and familial sources of contact; (b) Mantoux tuberculin test with increasing doses of old tuberculin (0.004 mg.; 0.025 mg.; 0.1 mg.; 1 mg. and 10 milligrams); (c) Photofluorography and, in dubious cases, teleradiography; (d) G.P.I. inoculation of gastric contents of suspicious primaries.

In tables 2, 3 and 4 the x-ray findings were as follows: N=normal findings; HE=hilar enlargement without noticeable parenchymal lesions; S=shadows of hilar or para-hilar condensations.

All tuberculin tests were read in 48 hours and recorded according to the intensity of reaction as: hypersensitive (strong positive reaction with 0.004, 0.25 or 0.1 mg.); moderately sensitive (moderate reaction with 1 mg.); hyposensitive (small reaction with 10 milligrams); and anergic (no reaction with any dose, up to 10 milligrams).

The results of the Mantoux tests have been recorded on tables 2, 3 and 4 as follows: 3=hyperergy; 2=mesergy; 1=hypoergy, and 0=nonreactor.

All x-ray films were read by specialists, without the knowledge that these pictures belonged to vaccinated children. Retakes were made whenever a minor technical failure was observed. All children with suspicious tuberculin tests or radiography, were given a gastric lavage and consequent animal inoculation was made (three or four pigs). The presence or absence of tuberculosis to be proved by necropsy of the inoculated pigs. Periodic sputum examinations of the source cases and chest plates of all adult contacts in household, were made.

TABLE 2: Summary results of the follow-up of 18 children vaccinated with 590 mg. BCG by mouth and exposed from birth to the contact with sputum-positive patients. (Group 1, *pro parte*).

F O L L O W - U P †											
CASE NO.	SPUTUM-POSITIVE EXPOSURE		TUBERCULIN TESTS				X-RAYS		Gastric Contents Results	General Results	CHILDREN'S FINAL CONDITION
	Sources	Duration (in mos.)	Duration (in mos.)	Total No.	Tuberculin Sensitivity (per year)	Number of films	X-ray Findings				
157987	Father Sister	0/12 18/31	36	17	2-2-3-1	10	N-HE-HE	Neg./24th	+		Healthy
158100	Mother	0/3	37	16	2-2-3-2	12	N-HE-HE	-	+		Healthy
158455	Father	0/6	37	7	2-2-2	9	HE-HE-HE	-	+		Healthy
158604	Father	0/22	38	17	2-2-3	12	N-S-HE	Neg./20th	++		Healthy
158759	Father	0/16	39	7	2-3-3	7	N-HE-HE	Neg./27th	++		Healthy
159677	Aunt	0/10	37	15	3-2-1-0	12	N-N-N	-	-		Healthy
159631	Father	0/23	37	19	0-3-2	12	N-HE-HE	-	+		Healthy
159815	Father Uncle Mother	0/37 0/25 7/9	37	21	2-2-2-2	23	N-S-HE	Neg./30th Neg./32nd	++		Healthy
160953	Mother	0/24	34	14	2-2-2	10	N-HE-HE	-	-		Healthy

162653	Father	0/10	36	15	2-3-2	22	N-S-S	Neg./20th Neg./22nd Neg./23rd	++	Healthy
163470	Father Mother	0/30 13/29	36	14	3-3-2	11	N-HE-HE	-	+	Healthy
165818	Father Uncle	0/15 15/27	33	14	3-3-3	14	N-S-HE	-	++	Healthy
170107	Father	0/5	31	14	2-1-1	10	N-N-N	-	-	Healthy
170685	Mother	0/28	31	11	2-3-3	14	N-S-HE	-	+	Healthy
171454	Father Cohab.	0/2 12/13	30	19	2-2-1	12	N-N-N	-	-	Healthy
171518	Father	0/24	29	10	2-3-3	11	N-S-HE	Neg./16th	++	Healthy
172164	Mother	0/12	24	5	2-3	8	N-N	-	+	Healthy
177041	Father Uncle	0/13 18/26	26	8	2-3	6	N-N	-	+	Healthy

† In the column "Gastric contents," the abbreviated figures indicate the month of the children's life when the inoculation of their gastric contents were made.

In the column "General results," the mark ++ indicates suspicious roentgenological findings of primary tuberculosis on clinically healthy children; + equals tuberculin findings indicating only a presumptive primary infection with virulent tubercle bacilli the mark - indicates the apparent absence of primary infection.

The figures in the column "Tuberculin sensitivity" and the initials in the column "X-rays findings" are the abbreviations referred to in the text.

TABLE 3: Summary results of the follow-up (24 to 37 months) of 16 children vaccinated with less than 590 mg. BCG by mouth and exposed from birth to the contact with sputum-positive patients. (Group 1, *pro parte*).

F O L L O W - U P										
CASE NO.	SPUTUM-POSITIVE EXPOSURE		TUBERCULIN TESTS					X-RAYS		CHILDREN'S FINAL CONDITION
			Duration (in mos.)	Total No.	Tuberculin Sensitivity (per year)	Number of films	X-ray Findings	Gastric Contents Results	General Results	
(A) Concurrent vaccination with 490 mg. BCG										
161232	Gr. moth.	0/5	24	4	2-2	4	N-N	-	-	Healthy
165230	Father Uncle	0/3 0/2	36	3	?-1	4	N-HE	-	-	Healthy
163580	Father	0/24	25	6	2-3-2	4	N-HE-HE	-	+	Healthy
163991	Father Brother	0/3 10/35	35	15	2-3-2	11	N-S-N	Neg./13th	++	Healthy
166041	Father	0/15	27	6	2-3-3	7	N-N-N	-	+	Healthy
170760	Mother	0/3	31	21	1-0-0	13	N-HE-N	-	-	Healthy
177418	Uncle	0/10	26	6	0-0-0	4	N-N-HE	-	-	Healthy

(B) Concurrent vaccination with 390 mg. BCG

		0/1 12/24	37	23	2-2-2	12	N-N-N	Neg./18th		Healthy
158291	Father Cohab.								-	
169482	Aunt	0/4	29	13	2-0-0	8	N-N-N	-	-	Healthy
174929	Father	0/1	24	15	2-2	11	N-HE	-	-	Healthy

(C) Concurrent vaccination with 290 mg. BCG

		0/3	37	2	?-3-3	4	N-?-HE			Healthy
157741	Mother							-	+	
158144	Father	0/2	37	4	3-3-3	7	N-N-HE	-	+	Healthy
172885	Aunt	0/1	27	4	2-2-3	5	N-N-HE	-	+	Healthy

(D) Concurrent vaccination with 190 mg. BCG

		0/16	33	8	1-1-1	5	N-N-HE			Healthy
163655	Aunt							-	-	
176578	Uncle	0/1	27	6	2-3-3	4	N-HE-HE	-	+	Healthy
177272	Father	0/21	24	5	2-3	4	N-S-HE	-	++	Healthy

TABLE 4: Summary results of the follow-up of 27 children vaccinated with different doses of BCG (from 290 to 590 mg.) and exposed from birth to contact with tuberculous negative-sputum patients.

CASE NO.	SPUTUM-POSITIVE EXPOSURE		TUBERCULIN TESTS				FOLLOW - U P			CHILDREN'S FINAL CONDITION
	Sources	Duration (in mos.)	Duration (in mos.)	Total No.	Tuberculin Sensitivity (per year)	X-RAYS		Gastric Contents Results	General Results	
						Number of films	X-ray Findings			
(A) Concurrent vaccination with 590 mg. BCG										
159714	Aunt Mother	0/6 34/38	38	1	N-?-?	-	-	Healthy*
157888	Mother Father	0/26 25/30	35	8	3-2-2	5	N-HE-HE	-	-	Healthy
158116	Gr. fath. Gr.moth.	0/6 0/33	36	10	2-2-0	5	N-HE-N	-	-	Healthy
159754	Gr. fath Gr. moth. Mother	0/6 0/24 36/37	37	10	3-2-2	7	N-N-N	-	-	Healthy
160759	Father	0/24	25	15	2-0-2	10	N-N-N	-	+	Healthy
160942	Aunt	0/16	37	18	2-1-1	10	N-N-HE	-	-	Healthy
161121	Father	0/27	37	13	2-0-2	14	N-N-HE	-	+	Healthy
162223	Father	0/24	24	15	0-0-0	11	N-HE	-	-	Death**
162771	Father	0/12	36	1	2-?-?	3	N-?-?	-	?	Healthy***
163913	Father	0/28	28	7	2-2-2	6	N-HE-HE	-	+	Healthy
169084	Mother	0/24	29	13	3-2-2	10	N-HE-HE	-	+	Healthy
170598	Mother Gr. moth.	0/27 0/11	30	16	2-2-0	8	N-N-N	-	-	Healthy
170662	Uncle	0/16	31	8	2-2-2	6	N-HE-HE	-	+	Healthy
172703	Father	0/24	29	14	2-2-2	13	N-N-HE	-	+	Healthy

* Only periodical home visits, without medical examinations.

** Death on the 32nd month, from acute broncho-pneumonia following measles.

*** Only periodical health notifications were reported by the family living out of Rio de Janeiro.

(B) Concurrent vaccination with 490 mg. BCG

	Father	0/33	33	10	3-2-2	11	N-N-N	-	-	Healthy
160782	Father	0/33	33	10	3-2-2	11	N-N-N	-	-	Healthy

(C) Concurrent vaccination with 390 mg. BCG

	Mother	0/1	4	0	?	3	N	-	-	Death*
161189	Mother	0/1	4	0	?	3	N	-	-	Death*
162609	Uncle	0/18	24	10	2-2	6	N-N	-	-	Healthy
162722	Father	0/24	24	0	?	1	N	-	?	Healthy**
168280	Father	0/24	34	5	0-0-0	5	N-N-HE	-	-	Healthy†
170617	Father	0/24	24	3	0-0	3	?	-	-	Healthy***

* Death on the eleventh month, from acute dysentery disease.

** Only home visits (the child's father had a negative report of inoculation of gastric contents).

*** Healthy tuberculin-negative child, with deficient x-ray examinations.

† Whooping cough on the last roentgenological examination.

(D) Concurrent vaccination with 290 mg. BCG

	Aunt	0/15	26	0	?	1	N-?	-	?	Healthy*
160086	Aunt	0/15	26	0	?	1	N-?	-	?	Healthy*
161516	Aunt	0/27	27	3	?-2	4	N-HE	-	+	Healthy
165123	Uncle	0/1	25	3	0-0	3	N-S	-	++	Healthy
164896	Father Mother	0/27 0/27	27	4	2-1	4	N-HE	-	+	Healthy
168772	Uncle	0/1	24	6	1-0	2	N-N	-	-	Healthy
170439	Mother	0/1	3	0	?	2	N	-	-	Death**
170740	Mother	0/27	27	3	?-2-3	7	N-HE-HE	-	-	Healthy

* Only periodical home visits (non-cooperative family).

** Death on the seventh month from diarrhoea condition and alimentary toxicosis.

*** Death on the 32nd month, from acute broncho-pneumonia following measles.

*** Only periodical health notifications were reported by the family living out of Rio de Janeiro.

3) Results:

Tables 2, 3 and 4 summarize the results of the follow-up of all children studied, for a period varying from 24 to 38 months. Table 5 shows the final results of both groups studied.

4) Deaths During Period of Observation:

Only three children died (up to April 1948), and all of them were in group II, not in contact with open cases of tuberculosis. Necropsy could not be secured since these children died at home; however, their attending physicians arrived at the following diagnosis: dysentery enteritis, alimentary toxicosis, and acute bronchopneumonia following measles.

TABLE 5: Final findings of the 61 children orally vaccinated with BCG (concurrent BCG vaccination) and living together with familial sources of pulmonary tuberculosis (duration of the follow-up: 24 to 38 months).

Sputum-Positive Contacts (Group 1)						
Final Findings	BCG DOSES (mg.)					Total
	590	490	390	290	190	
— *	4	4	3	0	1	12
+ **	8	2	0	3	1	14
++ ***	6	1	0	0	1	8
Incomplete data †	0	0	0	0	0	0
Deaths ****	0	0	0	0	0	0
TOTALS	18	7	3	3	3	34

Sputum-Negative Contacts (Group 2)						
Final Findings	BCG DOSES (mg.)					GRAND TOTAL
	590	490	390	290	Total	
— *	5	1	3	1	10	22
+ **	6	0	0	3	9	23
++ ***	0	0	0	1	1	9
Incomplete data †	2	0	1	1	4	4
Deaths ****	1	0	1	1	3	61

* Absence of virulent infection.

** Tuberculin allergy suggesting only a virulent infection.

*** Tuberculin and x-ray findings of clinically healthy children suggesting the presence of active primary tuberculosis.

† Healthy children with an insufficient follow-up.

**** Deaths from acute disease occurred in children followed-up and apparently found free from primary tuberculosis.

Discussion

A) The follow-up of these 61 children for more than two years, have only a relative value. It should be considered as an initial tentative report on how to utilize the antituberculosis immunization in communities where there is still a deficiency in the social and medical facilities for segregation of contacts and where it is not possible to secure organization equal to that of countries where the epidemiologic curve of tuberculosis has already decreased to the "limit of basal disease" as said by Flatzek-Hofbauer. Although all cases of household contacts might be rare in other countries, they represent the common situation in Brazil, thus justifying the selection of this type and scheme of treatment. The most significant contribution of this vaccination technique was the inhibition of primary tuberculosis among the 34 cases of group I in spite of permanent exposure to open cases of tuberculosis, from birth to two years. No deaths occurred among these children, and the specific tuberculosis morbidity was reduced to just a few cases where there was radiologic and allergic findings which were interpreted as signs of initial forms of primary tuberculosis. These cases showed neither symptoms nor clinical signs of diseases, sputum or gastric tests remained negative for acid-fast bacilli and, a rapid, regressive radiographic improvement was observed.

Since the socio-economic level of all cases in group I was low, the first results obtained with the concurrent BCG vaccination deserve certain attention so that a wider use of this method of immunization can be secured and divulged in the future.

The findings among children of group II, in which the danger of contagion was reduced due to the absence of positive sputum, corroborate our point of view (findings of group I), insofar as morbidity and mortality are concerned. Furthermore, group II revealed a greater prevalence of hyposensitive and anergic tuberculin reactions than group I, after the first two years of life.

Although three deaths occurred in children of group II, the specific mortality from tuberculosis can be excluded among the 61 children vaccinated, since a definite diagnosis of nontuberculous disease had been reached before death. Under these conditions, in regard to mortality during the first year of life, the results obtained with this new method of immunization revealed a definite improvement in tuberculosis mortality. Carvalho, using Calmette's scheme, observed 4.68 per cent mortality under the same conditions of exposure in the first year of life.

Obviously, the fact that no deaths from tuberculosis occurred among these children during two years of observation (going into

three years now) has an important significance, especially when investigations are being carried out to determine the prevalence of tuberculosis mortality among non-vaccinated infants. After a five year period elapses, however, more conclusive results will be reached.

B) The number of non-vaccinated children was not equal to those who were vaccinated, however, both groups lived under the same type of socio-economic and exposure conditions. It seems that the best means of comparison between vaccinated and non-vaccinated persons are those which try to maintain the maximum of similarity between contagion-factor and susceptibility-factor. Because the contagion-factor is subject to multiple causes of variation from one sick person to another (as for instance: virulence and number of bacilli involved, type of parenchymal involvement, type of treatment, change of personal hygiene, change of chances and time of contagion, etc.) it is reasonable to admit that for purposes of demonstration, the use of the same source of contagion in relationship to two different individuals of unknown susceptibility should be preferred to the use of two different sources, living under different conditions and acting separately upon each of the susceptible persons. On the other hand, the susceptibility-factor depends on several known and unknown environmental and individual circumstances. Among them, the genetic factors stand out, both in humans and animals and they might break down or resist in different ways to the uniform influence of an isolated infectious source.

Theoretically, the unquestionable comparison of any antituberculous immunization in human beings would be ideal in identical (monozygotis) twins, of whom one would be vaccinated and the other not. Both would be exposed to the same source of contagion. Until such experiment is made possible, only a relative comparison can be secured by observing children belonging to the same family, therefore, under the same type of contagion. This familial control has been done in Brazil by Carvalho and others. The fact that these children under observation differ in age, and consequently have different individual resistance, is considered as inevitable causes of errors. Notwithstanding the diversity above described, the importance of the uniform familial characteristics and sources of contagion acting upon vaccinated children and controls seem to offer a better field of comparison, than when observing children of the same age but with no genetic relationship and submitted to different sources of contact. For these reasons, it is understandable that the comparison between individuals vaccinated and controls, during adolescence or early adulthood, does not offer satisfactory evidence to judge the efficacy of anti-tuberculous

immunization, as well as it would during infancy, when an increased susceptibility exists.

The above mentioned "increased-infant-susceptibility" and, the observation in Rio de Janeiro of a specific mortality of 4.68 per cent among newborn infants vaccinated only one time (no re-vaccinations), and that of 23 per cent among non-vaccinated babies exposed to tuberculosis, were considered as definite reasons to carry out this investigation (Concurrent BCG Vaccination) among children during their two first years of life.

CONCLUSIONS

1) In Rio de Janeiro, Brazil, the specific mortality from tuberculosis is higher than 20 per cent in the first year of life of those children who are exposed to tuberculosis contagion immediately after birth. The socio-economic level of a large part of the population and the welfare organizations are not yet adequate to provide facilities to isolate children from tuberculous families in a practical way.

2) The peroral BCG vaccination of children exposed to tuberculosis, in the first 10 days of life and with doses from 60 to 90 milligrams, apparently reduced the specific mortality from tuberculosis in the first year of life to 4.68 per cent.

3) This partial result speaks in favour of the necessity to enforce the BCG vaccination of newborns exposed to tuberculosis, and monthly re-vaccinations with 100 milligrams of BCG, up to the sixth month of life should be carried out when the source of infection still exists.

4) The monthly use of BCG reaching total doses of 190 and 590 milligrams of vaccine, in 61 children ranging from two to six months of age was carried out with good tolerance, and without any ill consequences to the children, both when the weight and the lymphatic system were concerned.

5) Of these 61 children, 34 (Group 1), were in contact at home with an open case of tuberculosis from birth up to 37 months. Twenty-two were exposed to only one source of infection; 11 to two sources; and one to three sources. All of these children lived under unfavourable financial and sanitary conditions.

6) In this vaccinated group, followed from 24 to 36 months by physical examinations, x-ray films, eventual bacteriological examinations and tuberculin tests (Mantoux), no deaths occurred, either from tuberculosis or any other illness.

7) During the observation period, eight children at one time or another showed suspicious radiologic findings of active primary tuberculosis, in coincidence with a hypersensitive allergic reaction to tuberculin, however, without any clinic or bacteriological evi-

dence of disease (on three gastric lavages). Fourteen other children had only strong positive tuberculin reaction and, were considered for this reason as having primary phase tuberculosis, although clinic or radiologic evidence of disease could not be detected. Twelve children showed no clinical or radiological signs of disease and the tuberculin reaction was moderate and of the regressive type, apparently failing to reveal the existence of active primary infection.

8) Twenty-seven children (Group 2), who received from 290 to 590 milligrams of BCG were exposed to sputum negative patients (direct smear or animal inoculation) or to patients without any expectoration. Twenty-one were exposed to one tuberculous person; four to two persons and, two to one closed case during the first days of life and to an open case in the second year of life.

9) Among the children of Group 2, two deaths occurred within the first year of life, but both children had negative x-ray films and were diagnosed before death as having alimentary toxicosis with diarrhea and dysenteric enteritis. Another child (32 months) without any x-ray, allergic, or clinical signs of tuberculosis died from post-measles bronchopneumonia two years after the source case had been considered clinically cured and had negative sputum as demonstrated by two animal inoculations.

10) Of the 24 other children in Group 2, four were healthy up to 36 months, but lack of cooperation on the part of the families later on, made impossible a definite conclusion in regard to their health. Of the 20 other children, one had transitory radiologic evidence of right para-hilar involvement, which was interpreted as active, regressive primary. Nine children had hypersensitive (strong) tuberculin allergy which was considered as a sign of primary infection, although the physical and radiologic findings were normal. Ten did not have any evidence of virulent tuberculous infection. All of these 24 cases were followed from 24 to 37 months.

11) The results obtained with the Concurrent BCG Vaccination, during two years of observation, seem to indicate that in the 61 cases studied (particularly the 34 newborns of Group 1), there was a considerable decrease in the incidence of primary tuberculosis among vaccinated children in contact with tuberculosis in their early life. Moreover, no deaths occurred in this group up to the second year of life and the occurrence of active primary infections was low, recognized only by radioscopy and positive tuberculin reaction. These results represent only the beginning of an investigation which will take into consideration the BCG vaccination in a manner not yet contemplated in human beings.

CONCLUSIONES

1) En Río de Janeiro, Brasil, la mortalidad específica de tuberculosis es más alta que el 20 por ciento en el primer año de vida. Las condiciones socio-económicas de una gran parte de la población y las organizaciones de beneficencia, no son aún adecuadas para proporcionar facilidades para evitar el contacto a los niños de las familias tuberculosas de modo práctico.

2) El uso peroral del BCG en niños expuestos a la tuberculosis en los primeros días de su vida y con dosis de 60 a 90 miligramos, aparentemente redujo la mortalidad específica de tuberculosis en el primer año de vida a 4.68 por ciento.

3) Este resultado parcial habla en favor de la necesidad de hacer que se vacune con BCG a los recién nacidos expuestos a la tuberculosis, y de que mensualmente se les hagan vacunaciones con 100 miligramos de BCG, lo que se llevará a cabo hasta los seis meses de vida cuando todavía existe la fuente de infección.

4) El uso mensual del BCG llegando al total de 190 y 590 miligramos de vacuna, en 61 niños de dos a seis meses de edad, fué llevado a cabo con buena tolerancia y sin malas consecuencias para los niños, tanto en cuanto al peso como en lo que al sistema linfático concierne.

5) De esos 61 niños (grupo 1), 34 estaban en contacto en las casas con un caso abierto de tuberculosis, ya sea desde el nacimiento y en adelante hasta los 37 meses. Veintidós fueron expuestos solamente a una fuente de infección; 11 a dos fuentes y uno a tres fuentes. Todos estos niños vivían bajo condiciones sanitarias y económicas desfavorables.

6) En este grupo de vacunados seguidos de 24 a 36 meses por examen físico, radiografías, exámenes bacterioscópicos de vez en cuando y pruebas tuberculínicas (Mantoux), no ocurrieron muertes ya sea de tuberculosis o de otra clase de enfermedades.

7) Durante el periodo de observación, 8 niños en un tiempo o en otro demostraron hallazgos radiológicos sospechosos de tuberculosis primaria activa, en coincidencia con reacción alérgica e hipersensitiva a la tuberculina, y sin embargo, sin ninguna evidencia bacterioscópica de la enfermedad (después de 3 lavados gástricos). Catorce niños además solamente tuvieron reacción positiva fuerte a la tuberculina y fueron considerados por esta razón como sufriendo tuberculosis primaria, aunque la evidencia clínica o bacteriológica de la enfermedad no se pudo encontrar. Doce niños no mostraron evidencia clínica o signos radiológicos de la enfermedad y la reacción de la tuberculina fué moderada, de tipo

regresivo aparentemente sin revelar la existencia de infección primaria activa.

8) Veintisiete niños (grupo 2) que recibieron de 290 a 590 miligramos de BCG, fueron expuestos a enfermos con esputo negativo (por frotis directo o inoculación de animales), o a enfermos sin ninguna expectoración. Veintiuno se expusieron a una persona tuberculosa, cuatro a dos y dos a un caso cerrado durante los primeros días de la vida y a un caso abierto en el segundo año de la vida.

9) Entre los niños del grupo 2, dos muertes ocurrieron dentro del primer año de vida, pero ambos niños tenían hallazgos negativos a los rayos X y fueron diagnosticados antes de la muerte, como teniendo una intoxicación alimenticia con diarrea y enteritis disintérica. Otro niño de 32 meses sin ningún hallazgo a los rayos X o alérgico, o signos clínicos de tuberculosis, murió de bronconeumonía después del sarampión, dos años después de que la fuente infecciosa se había considerado clínicamente curada y tenía esputo negativo demostrado por dos inoculaciones en animales.

10) De los 24 niños restantes en el grupo 2, cuatro eran sanos hasta los 36 meses, pero la falta de cooperación por parte de las familias después, hizo imposible una conclusión definitiva respecto de su salud. De los otros 20 niños, uno tuvo evidencia radiológica transitoria de afección derecha parahiliar, que fué interpretada como tuberculosis primaria activa regresiva. Nueve niños tenían reacción tuberculínica fuerte que fué considerada como signo de infección primaria, aunque los hallazgos físicos y radiológicos fueron normales. No tenían ninguna evidencia de infección tuberculosa virulenta. Todos esos 24 casos fueron seguidos de 24 a 37 meses.

11) Los resultados obtenidos con la vacunación BCG concurrente durante dos años de observación, parecen indicar que en los 61 casos estudiados (particularmente los 34 recién nacidos, grupo 1), hubo una disminución considerable en la frecuencia de la infección primaria tuberculosa entre los vacunados en contacto con tuberculosos al principio de su vida. Más aun, no ocurrieron muertes en este grupo hasta el segundo año de vida y la presencia de tuberculosis primaria activa fué baja, reconocida solo por radioscopia y reacciones tuberculínicas positivas. Estos resultados representan solo el principio de una investigación que se hará considerando al BCG de una manera que hasta ahora no se ha ensayado en seres humanos.

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Experience with BCG Vaccination in Cordoba, Argentina*

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I shall try to inform you about the controversial subject "BCG Vaccination," its use and results in our country. The epidemiological, clinical and anatomical investigations lately performed in different countries, with precise techniques and methods of undebatable value, have permitted us to confirm the importance of primary tuberculosis as the origin for initial forms of pulmonary tuberculosis, especially in the young adult. Both, the tuberculin testing and the roentgenophotographic methods used in places where chances of a primary infection in adults is great, permits us to consider the influence of the first infection as the origin of the disease. The tuberculin testing of individuals of ages varying from 10 to 16 years old showed a percentage of 42.8 reactors among those who live in the mountainous regions of Cordoba, and 49.2 per cent among those living in the city. The same testing in the age groups 16-20 showed a percentage of 47.3 reactors in the rural populations and 69.6 per cent in the city. In such conditions, the primary infection has a greater chance to influence the origin of pulmonary tuberculosis in the young adults and older adults.

In our former paper "The Beginning of Pulmonary Tuberculosis in the Adult" we have discussed the existence of pulmonary lesions detected in adults, after their conversion from non-reactor into reactors. In another paper, the "Anatomical Features of Pulmonary Tuberculosis and Its Epidemiological Relationships" we discussed necropsies performed in 231 adults who died of pulmonary tuberculosis; among them, 55 cases were found to be of the childhood type (23.8 per cent).

Our research in Rio Grande do Sul, Brazil, has allowed us to prove the existence of a high proportion of non-reactors to tuberculin among the population; more so, in certain rural areas, where the percentage of adult non-reactors reached 50.7 per cent. Our clinical research at the Sao Pedro Psychopathic Hospital in Porto Alegre (Brazil) revealed a high percentage of primary forms

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among the tuberculous inmates of that hospital. In Bangu, Federal District (Brazil), Dr. R. Fernandez found 22.9 per cent of primary phase tuberculosis among all autopsies performed in adults dying from tuberculosis in the hospital.

Our actual observation of the relationship between primary infection and the beginning of clinical pulmonary tuberculosis in the adult, permits us to assure that every young adult who is a non-reactor to tuberculin, must be protected against the danger of primary tuberculosis. We, therefore, think that BCG vaccination represents the most convenient method to avoid the danger of a primary infection in young adults. In Cordoba, BCG vaccination has gone through its experimental stage and its use is quite divulged. From 1935 through 1946, 50 per cent of the newborns in the city of Cordoba were vaccinated, reaching a total of 22,254 infants. This vaccination is given on a voluntary basis. The vaccination of non-reactor young adults has not yet been sufficiently divulged. Nevertheless, at the Centro de Asistencia Medico-Social de la Tuberculosis, the number of persons presenting themselves for vaccination progressively increases. The vaccination program for school children in Argentina, as well as in other Latin American countries, should be considered as of real importance due to the local epidemiological picture, mainly, when a primary infection at that age represents a danger not to be neglected. In our report to the Sixth Pan-American Congress of Tuberculosis, held in Habana, Cuba in January 1945, we discussed the use of peroral BCG vaccination with .20 mg. of vaccine in children and school children up to 13 years of age, and the use of intradermal vaccination in an orphanage with .15 mg. vaccine. The latter study began in 1938 and was conducted with control techniques and no tuberculosis deaths were observed.

The vaccination was performed in Cordoba in a great proportion of newborns who were given home care through the Asistencia Publica. This group belonged to the poorest strata of the population and the household conditions were not well known. Because of the fact that household conditions were not known, several newborns exposed to tuberculosis might have been vaccinated, however, our experience showed good results, even though we might have inoculated these exposed babies. We believe that isolation should be secured only when the newly vaccinated child is in danger of being exposed to tuberculosis in the household. The isolation of the vaccinated child up to the time when it becomes a tuberculin reactor is the right procedure and should be observed. The isolation of young non-reactors before vaccination, is observed as a preventive procedure of an unknown pre-allergic period. However, we think that in certain cases it is impor-

tant to vaccinate the children regardless of exposure conditions.

The intradermal injection of 0.15 mg. BCG was used routinely in most of the newborns and children vaccinated. The oral, subcutaneous, multiple puncture and scarification methods of vaccinations have been carried out only in a small number of individuals.

CONCLUSIONS

From comparative investigations carried out in vaccinated and non-vaccinated children the following conclusions have been reached:

a) The general mortality within the first year of life was 8.3 per cent among the vaccinated and 15.6 per cent among the control group;

b) A mild degree of tuberculin sensitiveness was prevalent among vaccinated in contrast to the strongly positive results of Mantoux tests sometimes found in children belonging to the control group;

c) Chest x-ray films made on the vaccinated group disclosed 57.5 per cent lesions among children exposed to tuberculosis and 18.9 per cent among noncontacts, while in the control group there were 74.3 per cent lesions among exposed children and 47.6 per cent among noncontacts. In addition, the x-ray findings of the vaccinated group proved to be less important than that evidenced in the non-vaccinated. When primary infection was observed among vaccinated children, only glandular involvement could be detected.

For the protection of the newborn, small children, school children, and young adult non-reactors, exposed or not to tuberculosis, the BCG vaccination represents a good weapon in the prophylactic campaign against tuberculosis. However, vaccination must be employed together with the other known measures used in the control of tuberculosis.

CONCLUSIONES

De las investigaciones comparativas llevadas a cabo en niños vacunados y no vacunados, las siguientes conclusiones han sido alcanzadas:

a) La mortalidad general dentro del primer año de vida, fué 8.3 por ciento entre los vacunados y 15.6 por ciento en el grupo testigo.

b) Un grado moderado de sensibilidad tuberculínica dominó entre los vacunados en contraste con los resultados fuertemente positivos de la reacción de Mantoux, a veces encontrada en niños que pertenecían al grupo testigo.

c) Las películas radiográficas hechas en el grupo vacunado, descubrieron 56.5 por ciento de lesiones entre los niños expuestos a la tuberculosis y 18.9 por ciento entre los no expuestos, en tanto que en el control fueron 73.3 por ciento de lesiones entre los expuestos y 47.6 por ciento entre los no expuestos. Además los hallazgos radiológicos del grupo vacunado demostraron ser menos importantes que los encontrados en los no vacunados. Cuando la infección primaria se observó entre los niños vacunados, solamente se pudo descubrir el crecimiento ganglionar.

Para la protección del recién nacido, niños pequeños, niños escolares y adultos jóvenes negativos a la tuberculina, expuestos o no a la tuberculosis, la vacunación BCG representa una buena arma en la campaña profiláctica contra la tuberculosis. Sin embargo, la vacunación debe ser empleada en conjunto con otras medidas conocidas para dominar la tuberculosis.

A Critical Analysis of BCG in the Prevention of Tuberculosis*

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Since the termination of the recent World War, scientific attention has once again been focused on BCG in the prophylaxis of tuberculosis. Numerous reports on experimental studies have appeared and campaigns to vaccinate all children with negative tuberculin tests have been initiated in various countries. In Russia all newborn children receive BCG. In Hungary, over 2,000,000 cases were vaccinated within recent years. Similar large scale projects are being planned in Austria, Bulgaria, Czechoslovakia, Greece, Italy, Poland, Roumania and Jugoslavia. Denmark and Sweden have been among the leaders in this effort.

However, in spite of this apparent wave of enthusiasm over the use of BCG, the subject is still highly controversial. Numerous queries are still being made concerning the safety and efficacy of the vaccine, the degree of immunity, as well as reasons why the vaccine has not been used more extensively in the United States.

It is the purpose of this paper to review the subject and attempt to find answers to the above questions in the light of our present knowledge.

Safety of BCG Vaccine

At present there is almost unanimous acceptance of the belief that BCG is entirely harmless when inoculated into human beings. In 1920, Calmette and Guerin reported the vaccine to be entirely non-virulent when given to guinea-pigs, rabbits, monkeys, dogs, horses and cattle.^{1,2} In the same year, Calmette and Guerin reported that intravenous inoculation of human beings with BCG also proved harmless.³ During the years that followed, a number of experimental studies on animals raised suspicions that the attenuated organisms in the vaccine might increase in virulence.^{4,5} However, further careful and painstaking studies failed to support

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these suspicions. In 1932, Mishulow, Park and Mellman⁶ reported that BCG bacilli isolated from lymph nodes draining the inoculation sites in children showed a decrease rather than an increase in virulence. It is also significant that of the many millions already vaccinated throughout the world, there has as yet been no authentic case of a tuberculosis death resulting from a virulent strain of BCG.

It may be stated, therefore, that BCG is an attenuated strain of the bovine tubercle bacillus in which the loss of virulence is complete and permanent and that its use in human beings is entirely safe.

Efficacy of BCG Vaccine

Since 1921 when Weill-Halle⁷ inoculated the first human being with BCG, approximately 9,000,000 people have received the vaccine throughout the world. The great majority of these vaccinations have been performed in Europe, Asia and Africa. A fairly large number have been performed in South America, but only a limited number in North America.

Numerous reports have been published concerning the efficacy of the vaccine, and with very few exceptions these reports have been favorable. However, the vast majority of these statistical reports have been very inadequately controlled. A detailed report of many of these studies was published in 1946.⁸ In many studies, controls were lacking entirely; in many, the tuberculosis mortality of the vaccinated children was compared with the tuberculosis mortality in previous years; in certain studies the controls consisted of cases where vaccination was refused; in other studies the controls came from a different locality; in many instances, the controls were less carefully followed than the vaccinated group. In one study, alternate children in the same families were vaccinated or used as controls, an experimental method which fails to consider the wide variation in the number of tubercle bacilli in the sputum expectorated by a single infected individual over a period of months and years. In most of the reported studies reliable diagnoses at death were unobtained.

Evidence of the efficacy of BCG in the prophylaxis against tuberculosis has been presented in three different manners:

- 1) The development of a positive tuberculin test with the assumption that a parallel immunity exists.
- 2) Differences in tuberculosis morbidity statistics of vaccinated and control groups.
- 3) Differences in tuberculosis mortality statistics of vaccinated and control groups.

The development of a positive tuberculin test is not by itself

sufficient evidence that an adequate degree of immunity has been attained by a person or experimental animal. The inoculation of dead tubercle bacilli will also cause the development of a positive reaction, although claims for the efficacy of dead tubercle bacillus vaccine have never received the attention or acclaim given BCG. The assumed relationship existing between skin hypersensitivity to tuberculin and immunity has even been questioned.

Differences in tuberculosis morbidity have also been presented as evidence of the effectiveness of BCG in preventing tuberculosis. These studies range from the early observations by Heimbeck beginning in 1924 on student nurses at the Ulleval Hospital in Oslo⁹ to the more recent studies of Ferguson¹⁰ on student nurses in Saskatchewan. These reports, claiming efficacy for the vaccine on the basis of a reduction in roentgenographic pulmonary tuberculous lesions cannot be considered as adequate evidence. The BCG vaccination serves as the primary complex of tuberculosis with the primary focus at the site of the inoculation. Therefore, one should not expect to find the typical pulmonary primary complex of tuberculosis with its benign exudative infiltration on later exposure to tuberculosis. From a roentgenographic point of view one should only judge the efficacy of BCG by its ability to prevent the caseous pneumonic type of reinfection tuberculosis, proven bacteriologically.

Within the past few years several controlled studies on tuberculosis mortality have been reported from the United States. These observations have been of children in New York City,⁸ Chicago,^{11,12} and on Indian reservations.¹³

The New York Study, instituted by Dr. William H. Park in 1926 was the pioneer BCG experiment in the United States. In the course of this experiment various methods of selecting adequate controls were considered. The use of other children in the same family as the vaccinated child as controls was held inadequate for reasons already stated. For a short time an attempt was made to use selective controls where cases were balanced according to exposure and social factors.¹⁴ This method of selection was soon abandoned as statistically unsound due to arbitrary ratings given. Until 1933 half of the cases referred from tuberculous homes were vaccinated, the others serving as controls. After 1933 the method of alternate selection was instituted. On the basis of the New York Study the following standards were set down as fundamental in the study of vaccine prophylaxis against tuberculosis:

- 1) Vaccine must be of standard potency.
- 2) Controls and vaccinated cases should:
 - (a) be selected by alternation to eliminate possibility of bias.
 - (b) have identical follow-up.

- (c) come from same locality.
- (d) come from similar age group.
- (e) come from similar racial group.
- 4) Contact with cases must be maintained.
- 5) Exposure conditions of cases must be known throughout the study period.
- 6) A reliable diagnosis of the cause of death must be obtained.

The results of the study in New York City prior to January 1, 1933 were extremely favorable. Before that date, the selection of cases for vaccination and controls was left to the discretion of the physician assigned to the case. Realizing that unintentional bias could enter in the selection of cases, the method of alternate selection was instituted on January 1, 1933.

The comparative results of the studies during the two periods are shown in Table I.

It would appear from the above statistics that after the institution of alternate selection there was little difference in the tuberculosis mortality of controls and vaccinated cases. However, although these results were obtained in a carefully controlled experiment they are, nevertheless, open to the following criticisms:

During the latter part of 1932, the BCG cultures were contaminated by molds, and various means were used and considerable effort expended before pure cultures were again obtained.⁸ It is not beyond the limits of possibility that the original culture of vaccine was diminished in potency following efforts to eradicate the molds although it still produced local lesions and positive tuberculin reactions.

In addition, in the New York Study, children were not separated for at least six weeks before the pre-vaccination tuberculin test

TABLE I
Comparative Results Before and After Alternate Selection

	Number of Cases	TUBERCULOSIS Number	DEATHS Per cent
December 15, 1926 to January 1, 1933 (before alternate selection)			
BCG Vaccinated	445	3	0.68
Controls	545	18	3.38
January 1, 1933 to January 1, 1944 (after alternate selection)			
BCG Vaccinated	566	8	1.41
Controls	528	8	1.51

to prevent inoculation during the pre-allergic phase of tuberculosis, and they were not separated for six to eight weeks after vaccination to permit the possible formation of adequate immunity before exposure to positive sputum. This procedure was found impractical for general adoption in New York City.

However, a certain limited number of cases happened to be separated for three months before and three months after vaccination. A similar separation occurred in the cases of certain controls before and after being selected for observation.

These results, presented in Table II, give some indication that BCG might prove of protective value, if such separations were feasible.

The study on American Indians by Aronson and Palmer¹³ was carried out on four widely scattered reservations in the United States and in 12 communities of Southeastern Alaska. The results as presented in Table III are most favorable.

TABLE II
Exposed Cases Separated Three Months Before and Three Months
After Being Vaccinated or Taken Up

	Number of Cases	TUBERCULOSIS DEATHS	
		Number	Per cent
Vaccinated	91	1	1.1
Controls	96	3	3.1

TABLE III
Results of BCG Studies on Indian Reservations

	Vaccinated Cases	Tuberculosis Deaths	Controls	Tuberculosis Deaths
Arizona				
Pima A	259	1	263	2
Pima B	95	0	86	2
Wyoming				
Shoshone	110	0	85	1
Arapaho	118	1	106	4
North Dazota				
Chippewa	170	0	162	0
Marty Mission	41	0	25	1
South Dakota				
Rosebud	260	2	266	6
Alaska	497	0	464	12

These studies, when appraised in accordance with the standards of BCG evaluation, as presented previously, deviate as follows:

Thirteen different lots of BCG vaccine were used, rather than all the vaccine being obtained from a single source. In one reservation the comparatively poor results obtained after using BCG are stated as being possible due "to the fact that the three lots of vaccine used on this reservation were prepared from a slow growing culture (on veal-potato media) in place of Sautons' media and probably contained many dead organisms."

The arbitrary rating given for degree of exposure of contact cases is also open to question as is the accuracy of diagnosis at death, in view of the published statement that "in the control group some of the deaths which were assigned to nontuberculous causes actually may have been a consequence of tuberculosis." Apparently, diagnoses at death were not checked by postmortem examinations, a necessary measure as demonstrated by the New York studies. In spite of these obvious statistical difficulties, however, the report is favorable and must be added to the long list of favorable studies.

The results of over thirteen years experience with BCG in the city of Chicago^{11,12} are also favorable. The Chicago study is well controlled with alternate selection of cases; with vaccinated children separated from the tuberculous focus before and after vaccination, and the controls separated for a similar period; and with both controls and vaccinated cases followed equally. However, in this study, over 300 children have been lost and exposure conditions are frequently unknown. The lack of knowledge concerning exposure conditions seems evident when one considers that in the "control contact" group 52.7 per cent had positive tuberculin reactions at 2 years of age. According to the published report¹¹ these children should only have been exposed to negative sputum since it is stated that "fortunately the state of Illinois forbids a child under 16 years of age to live with a tuberculous

TABLE IV
Results of BCG Studies in Chicago

	Non Contact Cases		Contact Cases	
	Vaccinated	Controls	Vaccinated	Controls
Total number of children	1,417	1,414	151	105
Deaths from tuberculosis				
Number	1	7	0	4
Rate*	0.17	1.16	0	14.09

*Rate per thousand person-years observation.

member who has positive sputum." Furthermore in the Chicago study no information is given concerning the racial proportion among the vaccinated and control groups, although seven of the ten tuberculous deaths, as reported in April 1946, occurred in negro children. But again, the results of this study are definitely favorable as shown in Table IV.

A well controlled study on the efficacy of BCG has been undertaken by the U. S. Public Health Service at Columbus, Georgia. However, it will be some years before any adequate results can be obtained.

The results of BCG vaccination in Scandinavia which were also reported as favorable, are in most instances either inadequately controlled or entirely lacking in controls. A recent paper¹⁵ has presented the results of these studies. In both Oslo and Bergen, Norway, the tuberculosis mortality of the vaccinated group was compared with that of the general population. In Stockholm, Sweden, excellent results have been reported by Wallgren. In answer to objections that no controls were used, Wallgren stated that parents very seldom refuse to consent to BCG vaccination.¹⁵ Other studies in Sweden at Norbotten, Orebro and Boraas were also controlled by the general population. In Denmark, where the vaccination has been used extensively, controls are almost entirely lacking.

Degree of Immunity Conferred by BCG

The consistency of reports favorable to BCG, in spite of the paucity of accurate scientific analysis, would suggest that a certain degree of immunity against the development of primary tuberculosis is conferred. The degree of this immunity has not as yet been determined.

Wallgren,¹⁶ after reporting favorably on the effects of BCG, stated "On the other hand one should not exaggerate the effectiveness of BCG vaccination. At best it may protect against the immediate consequences of virulent infection and diminish the incidence of primary and early post-primary tuberculosis. In my own opinion there is no evident prophylactic influence on the development of late manifestations of post-primary tuberculosis, e.g., bone and joint tuberculosis; genito-urinary tuberculosis and late tertiary pulmonary tuberculosis."

The degree of immunity conferred by BCG vaccination is probably largely dependent upon the potency of the vaccine, the method by which it is used, the amount of vaccine used, the age of the vaccine, and possibly on the race of the person vaccinated.

The fact that BCG cultures may vary in their ability to produce local lesions and may differ in their immunizing quality has been

suggested by experimental work on animals and by studies on human beings.^{7,18} Moreover, it has been demonstrated that the vaccine becomes less potent the longer it remains in suspension. For example, the freshly prepared vaccine in suspension has considerably greater ability to produce local lesions and sensitization to tuberculin than vaccine used 7 to 10 days after preparation.

The method by which the vaccine is used is also an important factor. The oral method of vaccination used originally in Europe and in experimental work in the United States was discarded when it was shown that less than 60 per cent of those vaccinated developed positive tuberculin reactions as compared to over 90 per cent when vaccinations were performed parenterally.^{12,19} In spite of these findings the oral method of vaccination is still being used in certain countries of South America,^{20,21} although the dosages used are higher than those originally recommended by Calmette.

There are even questions raised concerning a difference in possible immunizing qualities of the vaccine in different racial groups. It has been suggested for example that the vaccine has greater activity when given to Negroes and Indians than when given to those of white origin. To date no studies have been reported bearing directly on this racial factor.

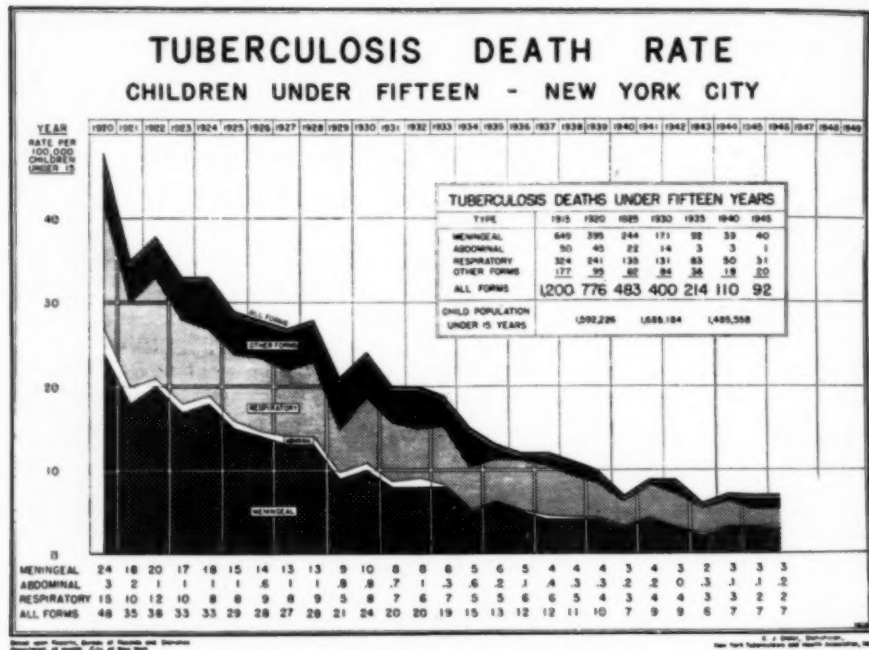
Duration of Immunity Conferred by BCG

On the basis of the numerous favorable reports on the efficacy of BCG it appears evident that some degree of incomplete immunity does exist following vaccination. The duration of such an immunity is again unknown. Although it is generally felt that some BCG immunity is present once the skin shows a tuberculin sensitivity following vaccination, it is not accepted generally that tuberculin sensitivity and immunity are necessarily concomittant. However, lacking specific knowledge, most workers have advised that tuberculin sensitivity be maintained, and that revaccination should be instituted if tuberculin allergy disappears.

The Status of BCG in the United States

In view of the enthusiasm with which BCG has been adopted as an anti-tuberculosis measure in various countries of the world, it has been asked on numerous occasions why it has not been so adopted by the United States. There are several obvious reasons for this attitude. In the first place, in the United States anti-tuberculosis measures such as case detection; separation of contacts; hospitalization; mass x-ray studies; tuberculin testing of

cows; and pasteurization of milk, have attained a high degree of success. As an example, one might take the city of New York with its crowded living quarters and with a negro population of over 540,000 as well as a large Puerto-Rican population. In this city as shown by the accompanying chart, the tuberculosis mortality of children under the age of 15 years has fallen 92.5 per cent



since 1915, a fall from 1200 deaths in 1915 (81 per 100,000) to only 92 deaths in the year 1945 (7 per 100,000) using only the usual well established antituberculosis methods. In the United States as a whole, the tuberculosis mortality has dropped from 202 per 100,000 in 1900 to only 36.4 in 1946.

It is not difficult to understand, therefore, why a prophylactic measure although falling short of complete immunity should be grasped at more avidly in countries where other antituberculous measures are difficult to carry out.

Bueno,^{20,21} in reporting on efforts toward the control of tuberculosis in Brazil writes "Because we do not have sufficient beds to isolate the sick, we try to use some more economical measure, which *for us* is more practical. In view of this situation," he continues, "the majority of specialists in Latin America and especially in Brazil favor vaccination with BCG." The same attitude is undoubtedly taken by many of the European countries that underwent the ravages of the past war.

The Potential Value of BCG

It must be acknowledged that the introduction of BCG into the body either orally or parenterally produces a primary tuberculous focus with an accompanying primary complex outside the lung parenchyma. The value of BCG, therefore, should rest on its ability to prevent complications and sequellae of the primary pulmonary complex of tuberculosis, such as the forms of hematogenous tuberculosis so often found in infancy, as well as the progressive primary focus.

Certain workers have claimed that the progression of the pulmonary primary focus to cavitation is a much more common occurrence in adolescents and young adults than during infancy and childhood.^{15,22} If this impression is correct BCG should be of particular value in protecting this age group from such a complication. However, this impression of the frequency of progressive primary tuberculosis in adolescents and young adults has not as yet been proved statistically.

The assumption that a parallel immunity to tuberculosis exists following the development of tuberculin skin sensitivity after vaccination has already been discussed. However, a positive tuberculin test following vaccination indicates that a primary complex has been present in the body and, unless contact with human tubercle bacilli has occurred, this primary complex is due to BCG.

If one assumes that a primary complex which has completely subsided gives some degree of protection against further exogenous tuberculous infections, then the rationale of inoculating negative tuberculin reactors with BCG appears evident. However, this subject is still controversial although the opinion stated is held by many workers in the field of tuberculosis.

Conclusions

It would appear that considerable further knowledge concerning BCG is necessary before it is accepted for general use in the United States.

Further knowledge is needed concerning (a) the actual degree of immunity conferred by the BCG vaccine, (b) the duration of immunity following vaccination, (c) the optimum method of administering the vaccine, (d) the effectiveness of the vaccine under varying degrees of exposure, (e) the effectiveness of the vaccine in different racial groups with various degrees of resistance, (f) the effectiveness of the vaccine when given to different age groups, and (g) the effectiveness of the vaccine when prepared with different culture media.

Further knowledge is also needed concerning methods of stab-

ilizing the potency of the BCG vaccine. On this particular point it might be noted that Dr. J. Orskov, member of the Expert Committee on BCG of the World Health Organization believes that it is impossible to achieve a real standardization of BCG vaccine. Making any vaccine, he claims, that will be uniform every time cannot be done even when following explicit rules.²³ Until this knowledge is obtained it would seem advisable to limit the distribution of BCG to institutions where it could be recommended for experimental use on negative tuberculin reactors where exposure to tuberculosis is likely to occur, such as children from tuberculous homes, nurses, and medical students. It could also be used in selected population areas with high tuberculosis mortality rates.

SUMMARY

1) In spite of the present wave of enthusiasm over the use of B.C.G. in the prophylaxis of tuberculosis, the subject is still controversial.

2) The loss of virulence of the bovine tubercle organisms in B.C.G. is complete and permanent and the use of the vaccine in human beings is entirely safe.

3) Although many favorable reports have been published on the efficacy of B.C.G. vaccine these studies, with very few exceptions, have been poorly controlled.

4) A critical analysis is made of studies on B.C.G. reported from New York City, Chicago and from various Indian reservations.

5) The degree of immunity as well as the duration of the immunity conferred by B.C.G. has not as yet been determined.

6) The use of common antituberculous methods has been so successful in the United States that the need for a prophylactic agent such as B.C.G., is less acute than in countries lacking adequate antituberculosis facilities.

7) Before the use of B.C.G. vaccine can be accepted as a general public health measure, considerable knowledge is still necessary.

8) The B.C.G. vaccine can in no way be offered as a substitute for other antituberculosis methods so successfully used in this country. At best, it may be offered as a supplement to already existing control measures in the United States.

RESUMEN

1) A pesar de la presente onda de entusiasmo acerca del empleo de B.C.G. en la profilaxia de la tuberculosis, este asunto todavía es contencioso.

2) La pérdida de la virulencia de los bacilos tuberculosos bovinos en B.C.G. es completa y permanente y el empleo de la vacuna en seres humanos es enteramente inocuo.

3) Aunque se han publicado muchos informes favorables acerca de la eficacia de la vacuna B.C.G., con pocas excepciones, no han sido bien comprobados esos estudios.

4) Se hace un análisis crítico de estudios sobre B.C.G. llevados a cabo en las ciudades de Nueva York y Chicago y en varios territorios reservados para indios.

5) Todavía no se ha determinado ni el grado de inmunidad otorgado por B.C.G. ni la duración de la inmunidad así adquirida.

6) El empleo de los métodos antituberculosos comunes ha obtenido tan buen éxito en los Estados Unidos que la necesidad de usar un agente profiláctico tal como B.C.G. es menos urgente que en otros países que no cuentan con facilidades antituberculosas adecuadas.

7) Se necesitan todavía considerables conocimientos antes de que se pueda aceptar el empleo de la vacuna B.C.G. como medida general de higiene pública.

8) No puede ofrecerse la vacuna B.C.G. como sustituto por otros métodos antituberculosos usados con tanto éxito en este país. A lo más, puede ofrecerse como un adjunto a las medidas de control existentes en los Estados Unidos.

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Discussion: Symposium on BCG

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Dr. Levine has made clear to us some of the difficulties attendant upon BCG vaccination. This procedure is one of the most debated subjects of the present day. It seems strange that, despite the fact that upward of 20,000,000 have been so vaccinated, there has still been no large scale study pursued over a sufficiently long period of time and marked by the inclusion of carefully followed controls calculated to answer the questions which Dr. Levine poses. Dr. Levine has shown us some of the difficulties in carrying out a study which could hope to answer the questions regarding efficacy of BCG vaccination. The final answer will await the outcome of long-term studies, studies now in progress in the United States, as well as elsewhere. In the meantime, some administrative decision must be made as to how and where BCG vaccination can be used pending the final decision that only such long-term studies can give us. It is hoped that this seminar will assist us toward deciding these points which are of immediate concern in the tuberculosis control program.

SIR SIDNEY SEWELL, M.D., F.C.C.P.

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In Australia we have been giving nurses and medical students Mantoux tests for the past 12 or 14 years, and roughly this is the way it works out. About 20 per cent of them give positive Mantoux tests when they begin their nursing training or training as medical students; yet by the time they finish their courses they are up to about 80 per cent positive. These conversions have taken place during the time they have been working with patients. We went into this subject as an advisory committee on tuberculosis, to investigate various means that might be taken to prevent this high conversion rate. We all recognize that it is those who recently become Mantoux positive who are likely, within the next two years, to develop tuberculosis, secondary manifestations. They provide most of the cases among students and nurses who, later in their course, develop active secondary lesions in the lung or elsewhere. The Mantoux positive cases show a much better result, i.e., those who were Mantoux positive when they began hospital work.

We went over all the available work on BCG very carefully and were convinced by the results—as any reasonable man should be

convinced—that BCG is effective as a protector, as it converts Mantoux negative to Mantoux positive in four to six weeks. We have taken these Mantoux positive nurses and medical students and given them the opportunity of having BCG vaccination, which we have flown to us from Ottawa, and it is used within five days. It has produced positive reactions in four weeks in 97 per cent of cases who have been inoculated.

Were I to carry back the pessimistic views put forth by Dr. Levine I would be doing harm. I certainly favor the other measures, with x-ray examinations of in-patients and out-patients, but it will take a lot to convince me that the magnificent work of Aronson is not of value. No one of the case examiners knew which were vaccinated and which were not, and the results were tabulated at the end without prejudice by quite independent observers. BCG effects on the nurses in Canada, as reported by Ferguson, are equally convincing, as is also much of the work reported from Sweden and Denmark.

To say it is not fair to compare cases inoculated in one period of five years with those not inoculated over the previous five years is, to my mind, ridiculous; we are not guinea pigs. I would like to see BCG used on medical and student nurse personnel, particularly in hospitals where all cases are not x-rayed immediately upon entering the hospital.

Closing Remarks

Francis J. Weber, M.D., F.C.C.P., Washington, D. C.: In the course of this discussion, slides have been shown depicting the results of BCG vaccination conducted in the Scandinavian countries and also in the United States. The work in these areas reveals that BCG vaccination appears to exert a definite protective action at least during the first years after successful vaccination. The longest study (and the only one embracing unvaccinated controls kept under continuous observation) is that of Dr. Aronson conducted among American Indians. In this work Dr. Aronson used a BCG strain obtained from the Pasteur Institute in Paris. The vaccination resulted in a high proportion of tuberculin reactors following vaccination. Roughly, the unvaccinated group developed three times as many cases as did the vaccinated and more than eight times the number of deaths occurred. This is considered statistically significant and certainly at the 11 year mark, there is a definite difference in favor of the vaccinated. Dr. Aronson and his group are continuing to follow these persons in the hope that we can get the best possible answer for the long-term appraisal of the efficacy of BCG vaccination.

It should be remembered that it is no easy task to conduct the type of study that we want to do. Moreover, since tuberculosis is a long-term, chronic disease, the evaluation of it requires a period of many years. As I have mentioned, the American Indian study, which has reached the 11 year mark, is our longest controlled study so far. We fervently wish that we had a much longer study at our back in order to be in a better position to make recommendations.

It should be pointed out that probably no other preventive procedure has ever been subjected to such rigid conditions of trial. Certainly, smallpox vaccination was never studied in the same way, nor were other vaccination procedures. This attitude reflects how far we have come in our thinking as to how medicinal agents or disease preventive agents should be studied. In using BCG we want to make sure that what we are doing is right. Certainly, a good preventive agent is something that is desperately needed among certain of our population groups. But whatever preventive agent may be found, it is unlikely that we can ever relax in our regular control efforts. Certainly, even if BCG vaccination proves to be all that its proponents claim it is, we will still need to depend upon early detection of tuberculosis and prompt isolation of cases if we are to eradicate tuberculosis in the United States. It is not believed that we are far enough along in our evaluation of BCG to recommend it for use among the general population of the United States.

Streptomycin in Tuberculosis*

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Following the announcement by Schatz, Bugie and Waksman,¹ in January 1944, of the isolation of streptomycin and, shortly thereafter, the demonstration of the effectiveness of this antibiotic against tuberculosis,² a considerable literature accumulated attesting to the value of the agent in many forms of the disease. But much remains to be learned before streptomycin finds its proper place in the scheme of treatment of tuberculosis.

Plan of Study

Crystalline streptomycin† alone was used in 44 patients with advanced tuberculosis from mid-June 1947 to January 1948. To assess the immediate effects of the product, data were available on a control group of 31 patients which had received streptomycin hydrochloride or sulphate or calcium chloride from October 1946 to mid-June 1947. The status of this group was determined as of the time the streptomycin was discontinued. A report of the results in this group of patients is in preparation.³ In addition, 11 patients received crystalline streptomycin after having had variable periods of treatment with one of the other forms of streptomycin mentioned. Each of the three groups included patients with extrapulmonary as well as pulmonary tuberculosis. The control group received streptomycin every 3 hours, with the exception of 2 who received it every 4 hours; the groups treated with crystalline streptomycin received it every 4 hours. Otherwise, the regimen was practically the same in both. The patients were examined periodically by vestibular, audiometric and ophthalmologic tests for the purpose of detecting any possible acoustic and optic nerve disturbances. In a considerable number, streptomycin levels were determined in the blood serum and, in a large number, bacteriologic examinations were made of the sputum or gastric contents to test the resistance of the tubercle bacilli to streptomycin.

*From the Division of Pulmonary Diseases and the Laboratory Division, Montefiore Hospital, New York, New York. Presented at a symposium on "Streptomycin Treatment of Tuberculosis" held at the Montefiore Hospital, New York City, January 14, 1948.

†The crystalline streptomycin employed was supplied by Merck & Co., through the courtesy of James M. Carlisle, M.D., Medical Director.

The initial group, treated from October 1946 to mid-June 1947, consisted largely of patients of the Montefiore County Sanatorium which admits individuals with relatively good prognosis. It should be emphasized, however, that the patients selected for streptomycin had shown progression of the disease in spite of prolonged bed rest and, in many instances, collapse treatment. The majority of those who received crystalline streptomycin were patients who, because of the advanced nature of their disease or the presence of serious complications, did not qualify for admission to the sanatorium. These were treated in the city branch of the Montefiore Hospital. Some of the hospital patients were in particularly poor condition, the streptomycin being given more in the hope than in the expectation of obtaining any benefit. The sanatorium as well as the hospital groups included Negroes, Puerto Ricans and young Irish in whom tuberculosis is notoriously progressive. The hospital group included nine patients with diabetes, two of whom had been treated with other forms of streptomycin before receiving the crystalline product.

In evaluating the immediate therapeutic effects of streptomycin, emphasis was placed on the roentgen findings in comparative films of the chest taken every two weeks. Although symptomatic improvement was almost the rule, it did not play a determining part in the assessment. In many, the sputum and gastric contents failed to reveal acid-fast organisms at the conclusion of streptomycin treatment. This also was an incidental consideration because the patients had not been observed long enough to make the results of the bacteriologic findings conclusive. The assessment was conservative in terms of immediate results based on a background of experience in the management of similar types of patients with standard forms of treatment.

A rating of V.G. (very good) was given to patients who made striking roentgenographic improvement; G. (good), to patients who made a degree of recovery considerably beyond what was to be expected from conventional methods of treatment, including collapse measures, which some had already received; and U. (undetermined), to patients whose improvement could not be definitely ascribed to streptomycin. It might be mentioned, parenthetically, that if any of the forms of treatment employed in the past, such as tuberculin, salts of heavy metals or the sulfones, had brought about the degree of symptomatic improvement shown in the U. group, this alone would have endowed the agents mentioned with sufficient therapeutic value to have warranted their retention in the armamentarium against tuberculosis. A rating of W. (worse) was given a Negro girl of 19 years whose disease progressed in spite of combined streptomycin and pneumothorax

SUMMARY OF IMMEDIATE EFFECTS OF CRYSTALLINE STREPTOMYCIN

Crystalline Streptomycin	Number	Very Good (V. G.)	Streptomycin given 4 mos. or longer	Good (G.)	Streptomycin given 4 mos. or longer	Undetermined (U.)	Streptomycin given 4 mos. or longer	Worse (W.)	Streptomycin given 4 mos. or longer
Acute Exudative Pulmonary Tuberculosis	8	3	1	2	1	3	2	0	
Caseocavernous or Pneumonic Tuberculosis	6	2	2	1		2		1	1
Fibrocavernous Tuberculosis	5	0		0		5		0	
In Combination with, or Preliminary to, Collapse or Other Surgical Measures	11	2	2	7		2	1	0	
Tuberculous Laryngitis or Bronchitis	10	2	1	6		2		0	
Miscellaneous Tuberculous Involvements	10	1	1	5	1	4		0	
Tuberculosis and Diabetes	8*	3	1	3	2	2		0	
Indications for Streptomycin in 44 Patients	58	13 (22%)	8	24 (41%)	4	20 (35%)	3	1 (2%)	1
Crystalline Streptomycin and Other Forms of Streptomycin in 11 Patients	11**	3	3	3	1	5	4	0	

*One patient received noncrystalline streptomycin for two and a half weeks before admission to the hospital.

**One patient was a diabetic.

treatment. She later had cavernostomy and successful thoracoplasty.

Indications for Streptomycin Treatment

Crystalline streptomycin alone was tested in the following:

- 1) Acute exudative or predominantly exudative pulmonary tuberculosis of recent onset or recent exacerbations of the disease (8 cases).
- 2) Caseocavernous or pneumonic tuberculosis (6 cases).
- 3) Fibrocavernous tuberculosis (5 cases).
- 4) In combination with or preliminary to collapse or other surgical measures (11 cases).
- 5) Tuberculous laryngitis or bronchitis, usually associated with advanced pulmonary tuberculosis (10 cases).
- 6) Miscellaneous tuberculosis involvements: (a) meningeal tuberculosis in a child of 4 years; (b) tuberculous empyema or pyopneumothorax in 4 patients and (c) cold abscess and/or draining fistulas in 5 patients (10 cases).
- 7) Tuberculosis complicated by diabetes (8 cases).

In a number of instances two or more major indications for streptomycin treatment were present in the same individual. This explains the larger number indicated above although only 44 patients were treated with the crystalline compound (see Table). A group of 11 patients treated with crystalline streptomycin, after having received other forms of streptomycin, will be analyzed separately.

1. *Acute Exudative Pulmonary Tuberculosis:* Of the 44 patients treated with crystalline streptomycin alone, eight had acute exudative disease of comparatively recent onset. Three had complicating diabetes and one, ulcerative tuberculous bronchitis. In two the disease had been progressing in spite of pneumothorax treatment (Fig. 1) and in one, an exudative spread followed a contralateral thoracoplasty. In every instance the sputum was positive on direct smear and in three the disease was febrile before streptomycin was begun.

In five patients the initial dose was 1 gm. crystalline streptomycin daily, in divided doses every four hours. Because these patients did not seem to do as well on 1 gm. as others who were receiving larger amounts, after a trial period of five to eight weeks, the dosage was increased to 2 gm. per day. One received 2 gm. throughout the period of treatment and two received 3 gm. per day, for three months each. In the three to four months of treatment which these eight patients received, the dosage for the entire course averaged 190 gm. per patient.

The immediate effects were very good in three, good in two,

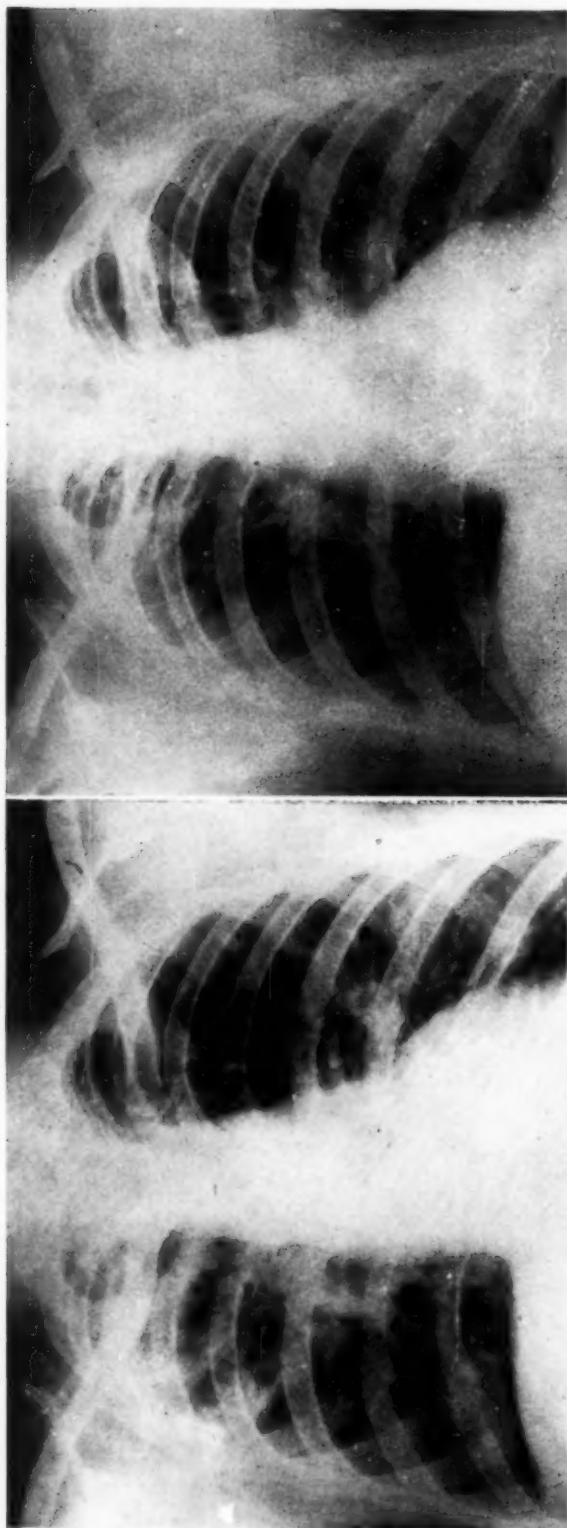


FIGURE 1A

FIGURE 1B

Fig. 1: Streptomycin treatment of exudative tuberculosis in a man of 32. Disease had progressed in spite of pneumothorax treatment. (A) Right upper lobe reveals soft confluent infiltrations with areas of cavitation; scattered infiltrations in left midlung. (B) After 3 months of crystalline streptomycin treatment (3 Gm. daily, 270 Gm. total) there is marked clearing of infiltrations in both lungs. Sputum and gastric concentrates negative for acid-fast organisms.

and undetermined in three. In the U. group there was considerable to marked symptomatic improvement in every instance in the way of lessened cough and expectoration, increased weight and general well-being. In one of the U. group the sputum became negative on concentrate although there were no significant changes in comparative roentgen films. With the exception of two patients who had practically no reactions, all had slight to marked dizziness. This, however, did not interfere with the treatment. The eosinophiles in the blood ranged from 5 to 21 per cent.

A comparable group of 11 patients with acute exudative pulmonary tuberculosis treated in the control group at the sanatorium revealed similar immediate effects, possibly better. In 6 patients the indications for streptomycin were recent spread of tuberculosis following hemoptysis or bronchoscopy or cavernotomy; none had diabetes, tuberculous bronchitis or other serious complications as were present in the hospital group. Of particular significance is the fact that in several of the control group streptomycin was given for comparatively short periods of time, the interruptions being caused by lack of antibiotic or because of toxic manifestations. Yet improvement continued in spite of curtailed treatment.

2. *Caseocavernous or Pneumonic Tuberculosis*: Six of the 44 patients treated with crystalline streptomycin had progressive caseocavernous tuberculosis. One was a diabetic, one had tuberculous empyema, one probable laryngeal tuberculosis and one tuberculous fibrous bronchitis. The majority were in the "ultimum refugium" class of patients (Fig. 2). It seemed hardly likely that any would be benefitted by the treatment. With the exception of one patient, a woman of 34 who received 1 gm. of streptomycin for a month intrapleurally for a tuberculous empyema and 2 gm. for two and a half months intramuscularly, the others received 2 gm. daily and, in one instance, 3 gm., for periods ranging from two to five months. An unusually large amount of streptomycin (300 gm.) was given for a period of five months to a Negro girl of 19, mentioned previously, who had caseocavernous tuberculosis. The cavities in both lungs became larger in spite of streptomycin and pneumothorax treatment. The total dosage in the six cases averaged 230 gms.; the smallest individual total dose, 170 gm.; the largest, 306 gm.

The immediate effects in this group were very good in two patients, good in another, undetermined in two and, in the Negro girl, the condition became worse. The last-mentioned is the only instance among the 44 treated with crystalline streptomycin in which at least a halt in the downward course of the disease was not realized. In none other did the disease progress while the

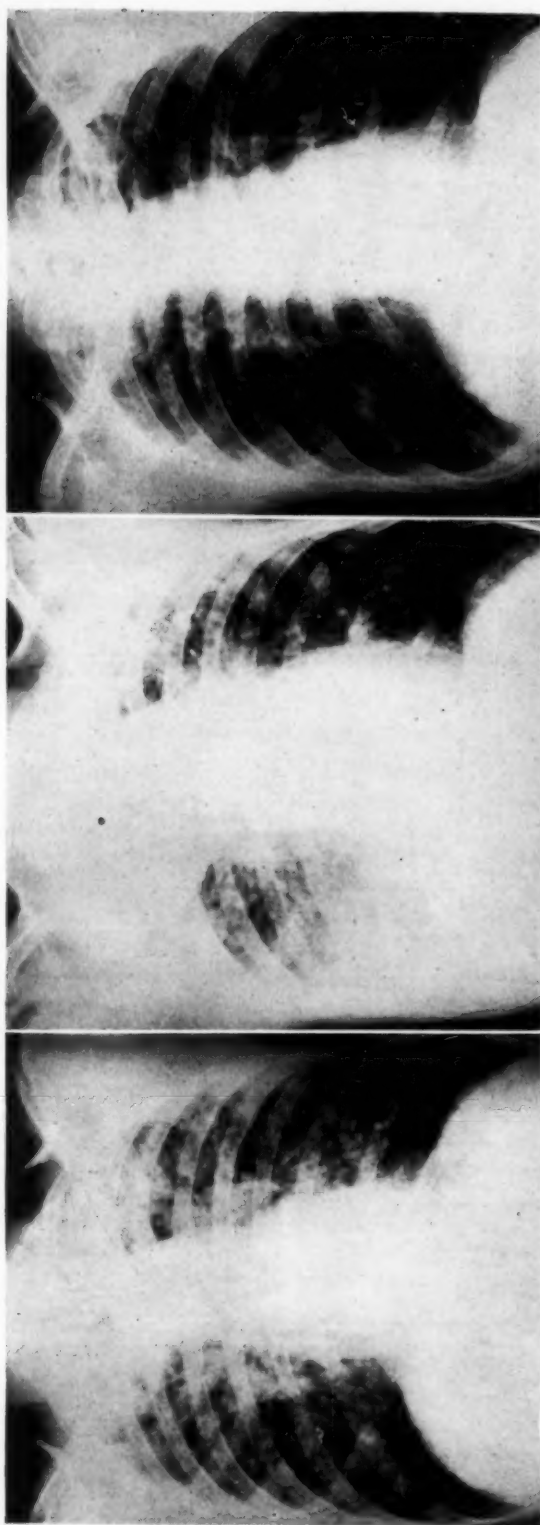


FIGURE 2A

FIGURE 2B

FIGURE 2C

Fig. 2: Streptomycin treatment of caseocavernous and laryngeal tuberculosis in a man of 43. Disease had been progressive on bed rest. Prognosis hopeless. (A) Disseminated infiltrations throughout both lungs with cavitation in the upper lobes. (B) Two months later there is consolidation of right upper lobe and pleural effusion at base; increased density in left upper lobe with enlargement of cavity. (C) After 4 months of crystalline streptomycin treatment (2 Gm. daily, 240 Gm. total) there is marked clearing in both lungs with absorption of fluid and disappearance of cavities. At time of discontinuation of streptomycin, sputum still positive on culture.

patient was under streptomycin treatment. The side reactions in this group were more pronounced than in the preceding one. The dizziness was more severe and, in one instance, there was a desquamating erythema which appeared at the termination of the treatment. The eosinophiles ranged between 13 and 27 per cent.

Except for one patient who had tuberculous pneumonia in the course of protracted hematogenous tuberculosis and who made a striking recovery under streptomycin treatment, there were no patients in the control series who had disease of comparable degree as was encountered in this group.

3. *Fibrocavernous Tuberculosis*: Five of the 44 patients treated with crystalline streptomycin had fibrocavernous tuberculosis. Of these, two had residual cavities following incomplete thoracoplasty. Three were past 50 years of age; all had the disease for some years; all were afebrile and all had acid-fast organisms in the sputum or gastric contents. In two the dose was begun with 1 gm. per day and later increased to 2 gm. One patient, a diabetic, had another form of streptomycin for two and a half weeks prior to admission to the hospital. He received 1 gm. daily of the crystalline compound for six more weeks; the others had 2 gm. daily. The duration of treatment ranged from two to three months, averaging two and a half months. The total dose for the entire course of treatment averaged 140 gm. for each patient.

The immediate effects of streptomycin treatment could not be determined in any of the patients in this group although several improved subjectively and in one, gastric examinations failed to reveal acid-fast organisms. No less than four had marked side reactions in the form of dermatitis and dizziness; three had stomatitis of variable intensity. The eosinophile count ranged from 5 to 38 per cent. A comparable group of three patients with fibrocavernous tuberculosis in the control group gave equally inconclusive results.

4. *In Combination with or Preliminary to Collapse or Other Surgical Measures*: One of the most instructive groups treated with crystalline streptomycin consisted of 11 patients who received the treatment in conjunction with pneumothorax or thoracoplasty. Without streptomycin few would have had the benefit of collapse therapy. Two patients with bilateral exudative disease improved sufficiently to make possible the induction of pneumothorax on the more involved side. In one of these a tension cavity rendered the pneumothorax ineffective. The presence of advanced tuberculous laryngitis in one patient and tuberculous laryngitis and pyopneumothorax in another had precluded thoracoplasty. The former, an asthmatic to boot, showed spectacular improvement in the lungs and larynx following streptomycin treatment (2 gm.

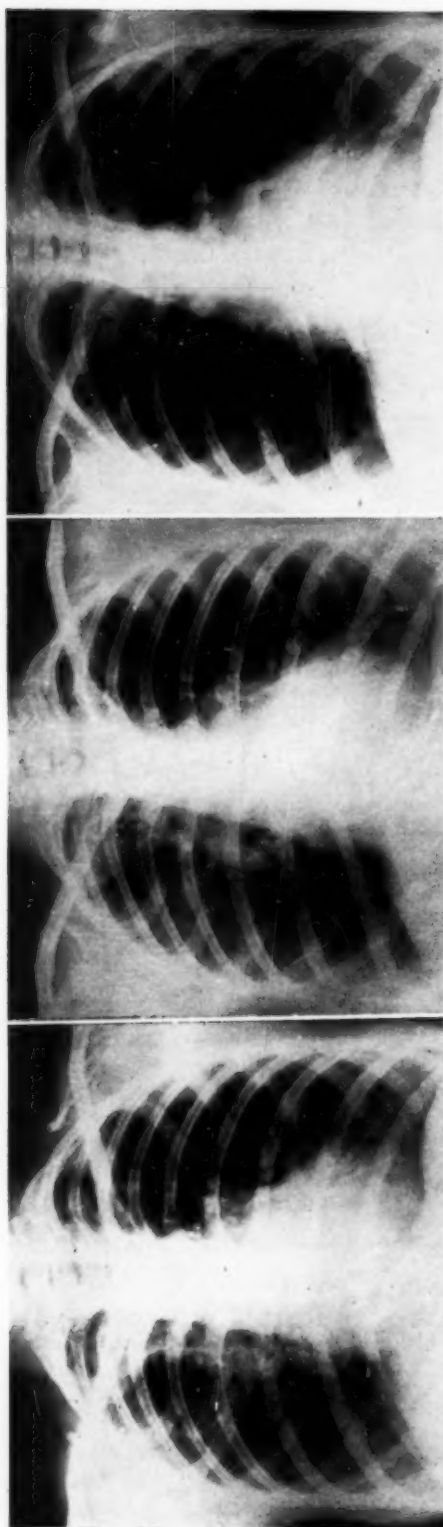


FIGURE 3A

FIGURE 3B

FIGURE 3C

Fig. 3: Streptomycin treatment, preliminary to a contemplated thoracoplasty, of an asthmatic girl of 21 who had advanced tuberculosis of the lungs and larynx. Disease progressive in spite of bilateral pneumothorax treatment. (A) Large cavity in right upper lobe and scattered infiltrations in lower lobes and left midlung. (B) After 4 months of crystalline streptomycin treatment (2 Gm. daily, 240 Gm. total) the cavity is no longer visible, the site occupied by a circumscribed density and linear infiltrations. (C) Three months after discontinuation of treatment there is practically no roentgenologic evidence of disease. Laryngeal tuberculosis healed; gastric contents failed to reveal acid-fast organisms on culture; thoracoplasty withheld because of unexpectedly good results. Six months after discontinuation of streptomycin treatment status unchanged. Gastric contents still negative for acid-fast organisms.

for 4 months). Gastric examinations failed to reveal acid-fast organisms. The contemplated thoracoplasty was withheld at the request of the patient (Fig. 3). Incidentally, several other patients refused thoracoplasty because of the improvement in their status. However, surgery was indicated and the patients were urged to submit to the operation. The patient with tuberculous laryngitis and pyopneumothorax, mentioned above, improved sufficiently to undergo thoracoplasty.

In two patients, one a diabetic, thoracoplasty is temporarily in abeyance because of unexpectedly good improvement. In four, one of whom had tuberculous pyopneumothorax, thoracoplastic operations were successfully completed (Fig. 4). One had an exacerbation of the disease in the contralateral lung two months later which subsided on bed rest. Crystalline streptomycin was given to one patient for 45 days to counteract a lower lobe spread of the disease following a first stage thoracoplasty. The second stage was completed and the patient is now convalescing. In evaluating the immediate effects of crystalline streptomycin in this group of patients, the deciding factor was whether or not the treatment accomplished its purpose, and how well. Obviously it was impossible to judge this on the basis of the streptomycin treatment alone.

The amounts of streptomycin given in this group of patients varied considerably depending on individual indications. The smallest amount dispensed was 45 gm. for an equal number of days; the largest amount, 320 gm. for five and a half months. The toxic reactions in this group of patients were moderate. In three there were no significant side effects and in one a severe dermatitis developed which did not interfere with the treatment. The eosinophile percentage ranged from 5 to 33. A group of seven patients in the control group to whom streptomycin was given for similar indications gave equally good results.

5. Tuberculous Laryngitis and/or Bronchitis: Ten patients of the 44 had as their major indication for streptomycin treatment tuberculous laryngitis or bronchitis or both. One had, in addition, tuberculous sinuses draining in the chest wall; another, pyopneumothorax. All but two had pulmonary tuberculosis of considerable degree. Two patients received 0.5 gm. of streptomycin daily by inhalation, in addition to intramuscular injections. The patient with pyopneumothorax received instillations of 1 gm. streptomycin intrapleurally for two months, in addition to intramuscular injections. The duration of the intramuscular treatment for the group ranged from two and a half to four months. The average total intramuscular dosage, with the exception of one still under treatment, was 150 gm.



FIGURE 4A

FIGURE 4B

FIGURE 4C

Fig. 4: Streptomycin treatment of advanced pulmonary tuberculosis and tuberculous pyopneumothorax in a man of 36. Successful thoracoplasty. (A) Caseocavernous tuberculosis occupying the greater part of the left lung; exudative tuberculosis of the lower half of the right upper lobe. (B) Nine months later, after a trial of pneumothorax treatment, there is a density occupying the left hemithorax due to thickened pleura encasing a tuberculous lung and empyema; considerable absorption of infiltrations in right lung. (C) After a course of crystalline streptomycin intrapleurally and intramuscularly for a total period of 6 months (320 Gm.) during which a three-stage thoracoplasty was completed. Four months after the discontinuation of active treatment, sputum is negative on concentrate and there is continued improvement in right lung.

The effects of streptomycin in one patient with extensive tuberculous bronchitis was equivocal (U.); in another, the sinuses of the chest wall closed but the laryngeal lesions remained unchanged (U.). One patient with tuberculous laryngitis, tuberculous pyopneumothorax and cavitary tuberculosis improved sufficiently (G.) to allow the performance of a thoracoplasty. Of the remaining seven, there was considerable to complete healing (G.) in five and excellent immediate results (V.G.) in two. In one of the latter, a large cavity in the right lung closed and ulcerative tuberculous bronchitis healed. The sputum became negative on concentrate. Noteworthy is the fact that this patient had only 1 gm. of streptomycin for four months. In four patients who had positive sputum before treatment and whose laryngeal or bronchial disease improved, the sputum became negative on concentrate or culture at the conclusion of treatment. Two others had apparently arrested pulmonary tuberculosis as indicated by the negative sputum and appearance of the roentgenogram prior to the institution of streptomycin treatment. Both had active tuberculous laryngitis which healed under streptomycin treatment.

The side reactions were slight to moderate in all but one. This patient, a woman of 46 years, had severe dizziness, stomatitis and the highest eosinophile count (67 per cent) encountered to date in any of our patients. No significant change was observed in the extensive ulcerative tuberculous bronchitis which involved the major bronchi of the right lung.

A comparable series of six patients in the control group revealed similar findings. Mention will be made later of the occurrence of asthmatic symptoms in several patients who received streptomycin by inhalation.

6. *Miscellaneous Tuberculous Involvements:* Crystalline streptomycin was given intrathecally (0.1 gm. daily, later at longer intervals) and 1 gm. daily intramuscularly to a child of four years with tuberculous meningitis, treated on the Pediatric Service of the Morrisania City Hospital. The diagnosis was confirmed by the finding of acid-fast organisms in the spinal fluid. The child's mother had tuberculosis and a brother of six and a half years had died of tuberculous meningitis. On admission to the hospital the child was acutely ill, febrile, and had a left hemi-paresis. Intrathecal streptomycin was maintained for four months and intramuscular streptomycin for six months. At the time of writing the child's condition is much improved. She is alert, active, and cheerful. She is able to walk with assistance, and is receiving physiotherapy for the hemi-paresis, which has persisted.

Four patients with tuberculous empyema or pyopneumothorax were treated with crystalline streptomycin intrapleurally (1 gm.

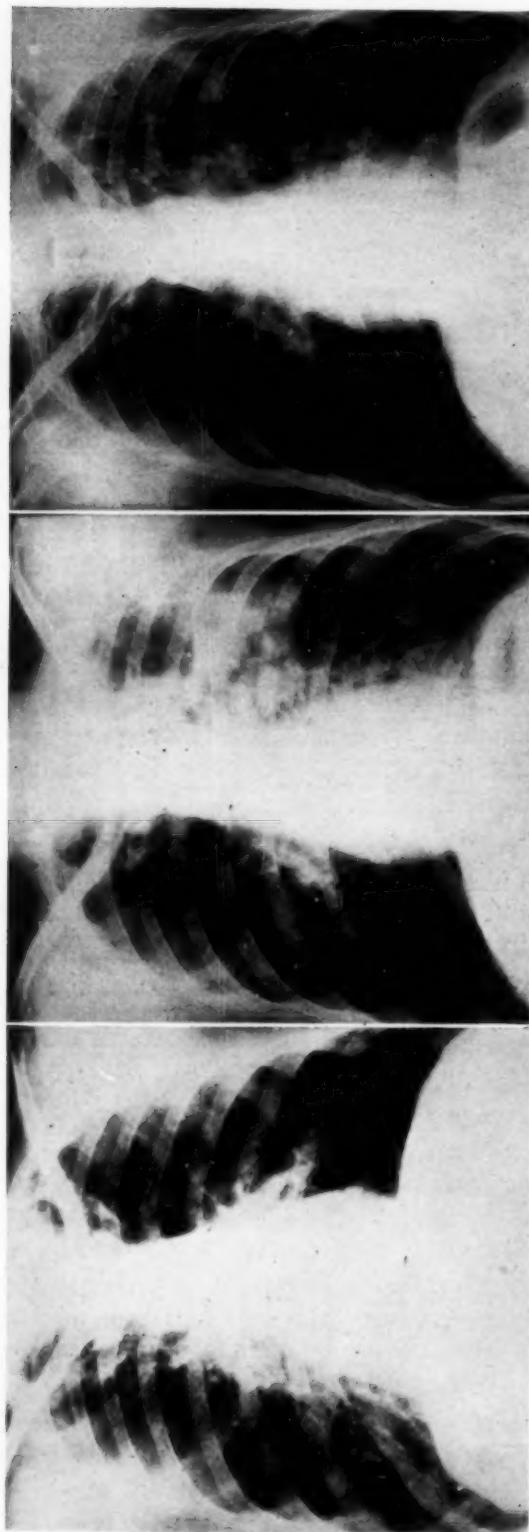


FIGURE 5A

FIGURE 5B

FIGURE 5C

Fig. 5: Streptomycin treatment of caseocavernous tuberculosis in a diabetic man of 63. (A) Routine x-ray film of chest prior to development of tuberculosis reveals no gross pathologic changes. (B) Left upper lobe is now occupied by a giant cavity showing a fluid level in a caseous lung; disseminated infiltrations in lower lobe. (C) After 4 months crystalline streptomycin treatment (2 Gm. daily, 240 Gm. total) there is marked clearing and the cavity is no longer seen. Sputum negative on concentrate and culture on repeated examinations; disease arrested.

instillations) as well as intramuscularly. In two it may have helped to prepare for successful thoracoplasty; in the other two, no significant changes were noted. Five patients with draining fistulas were treated with crystalline streptomycin. In one, the fistula closed temporarily, and then permanently; in another, a post-thoracoplasty fistula that had been draining for four years closed and was excised surgically. In the remaining three, the fistulas closed in from four to six weeks; in two, however, they have recently reopened.

7. *Diabetes and Tuberculosis*: Montefiore Hospital admits a considerable number of patients with tuberculosis and diabetes. This accounts for the fact that eight patients with both diseases were treated with crystalline streptomycin. An additional patient, a woman of 35 years, with severe diabetes, caseocavernous tuberculosis and tuberculous bronchitis was treated with other forms of streptomycin for four months (1-2 gm. daily) prior to receiving crystalline streptomycin for an additional two months. In all, the patient received 370 gm. for six months, the largest amount of streptomycin given to a single patient in our investigation to date. An advanced tuberculous lesion in the left lung cleared satisfactorily, as did the laryngeal lesion. Because of the low vital capacity and poor physical condition, the patient was not considered a good risk for thoracoplasty. However, it was possible to perform a cavernostomy for a large cavity in the right lower lobe.

Of the eight patients with tuberculosis and diabetes, treated with crystalline streptomycin, three did exceptionally well (V.G.). In a man of 32 years whose tuberculosis was getting progressively worse in spite of pneumothorax, the disease apparently became arrested after a course of streptomycin (3 gm. for 3 months). Another man of 31 years who received 3 gm. for three months showed healing of a large cavity in the right upper lobe and conversion of the sputum. A dramatic improvement occurred in a diabetic man of 63 years (Fig. 5). He had caseocavernous tuberculosis with a giant cavity occupying almost the entire left upper lobe. Before crystalline streptomycin was administered he was expectorating more than two boxes of purulent sputum daily. After four months of treatment (2 gm. daily), the cavity in the left upper lobe disappeared in the roentgenogram and the minimal amount of sputum which he raised failed to reveal acid-fast organisms on repeated examinations by concentrate and culture. Satisfactory improvement was noted in three patients (G.) and no apparent response (U.) in two others. This group did remarkably well considering the serious nature of the disease in every one of the patients treated.

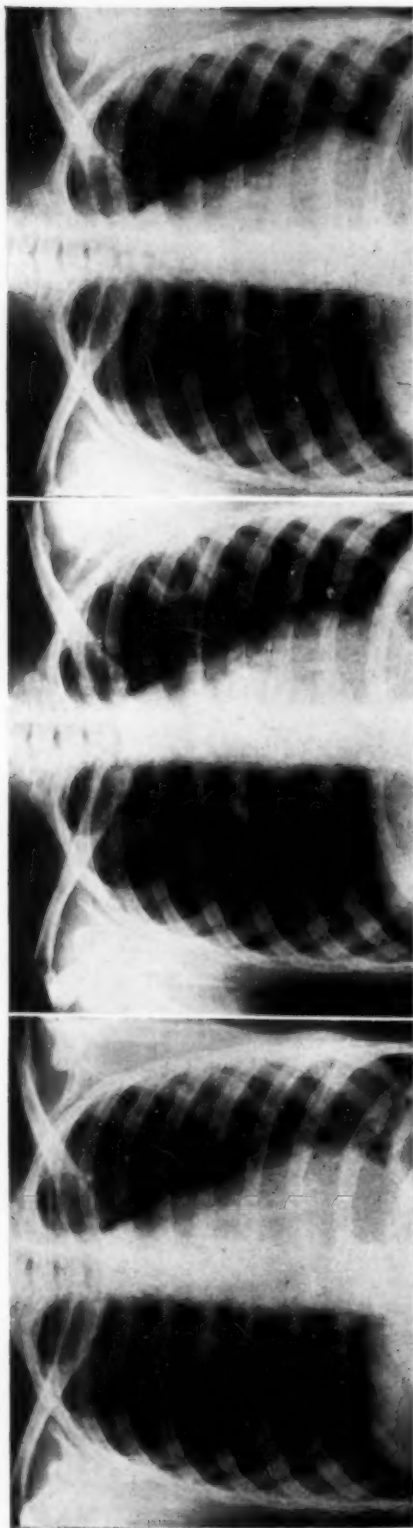


FIGURE 6A

FIGURE 6B

FIGURE 6C

Fig. 6: Streptomycin treatment of an epileptic girl of 19 with progressive bilateral tuberculosis to clear disease in one lung preparatory to a contemplated thoracoplasty on the other. Surprisingly good results made operation unnecessary. (A) Exudative tuberculosis in left lung with cavitation in upper lobe. (B) Ten months later, while on rest regimen, cavity in left upper lobe considerably larger; fresh infiltrations in right lower lobe following hemoptysis. (C) After 5 months streptomycin treatment, including 3 months with the crystalline compound (1-2 Gm. daily, 225 Gm. total) complete clearance of infiltrations; cavity not visible; sputum negative for acid-fast organisms on concentrate and culture. Six months after discontinuation of treatment, gastric cultures negative; disease apparently arrested.

*Crystalline Streptomycin After Other Forms of Streptomycin
Had Been Applied*

Crystalline streptomycin was given to 11 patients after they had received previously other forms of streptomycin for variable lengths of time. In three, no interruption occurred in the course of treatment. In one, there was an interval of nine days and in another, a diabetic woman of 35 years, referred to previously, 15 days; in the remainder, six weeks to seven months elapsed. In the patient in whom there was an interval of only nine days, streptomycin was given (1-2 gm. for 4 months, 175 gm. total) preliminary to thoracoplasty. However, he did so well that thoracoplasty was withheld. In the three patients in whom no interruption occurred between courses of treatment, streptomycin was given in one to clear contralateral active tuberculosis preliminary to thoracoplasty (2 gm. for 5 months, 225 gm. total) (Fig. 6). Thoracoplasty was withheld because of the unexpectedly good results, the roentgenogram revealing apparent arrest of the disease and the sputum failing to reveal acid-fast organisms on concentrate and culture. In another, a girl of 21 years, streptomycin prepared a poor risk for a successful thoracoplasty. In the third, a man of 34 years with extensive tuberculous ulceration of the buccal mucous membrane and miliary tuberculosis of the lungs, streptomycin HCl (2 gm. daily in divided doses, every 6 hours) had been given for six weeks prior to admission to the Montefiore Hospital. By the time he entered the hospital, the oropharyngeal lesion had healed completely but the miliary infiltrations in the lungs showed conglomeration. He was given 1 gm. of crystalline streptomycin for two more months and then the dose was raised to 2 gm. for another six weeks. By the time the streptomycin was discontinued the pulmonary infiltrations were no longer visible in the roentgenogram. He was discharged and is now attending the out-patient clinic (Fig. 7).

In six patients in whom considerable time elapsed between the noncrystalline and crystalline streptomycin applications, the following was noted. A girl of 17 years received 270 gm. (3 gm. daily for 3 months) of a noncrystalline form of streptomycin. After an interval of 2 months she received 1 gm. daily of crystalline streptomycin for an additional two months (70 gm.). An active tuberculosis lesion cleared in the left lung and a successful three-stage, seven-rib thoracoplasty was performed on the right side (Fig. 8). A Puerto Rican girl of 17 years with bilateral exudative tuberculosis had been treated for five weeks with 2 gm. daily of a noncrystalline form of streptomycin (70 gm.). After an interval of five months, crystalline streptomycin, 2 gm. daily, was



FIGURE 7A

FIGURE 7B

FIGURE 7C

Fig. 7: Streptomycin in treatment of acute miliary pulmonary and ulcerative oropharyngeal tuberculosis in a man of 34. (A) Miliary tubercles evenly disseminated throughout both lungs (they can hardly be seen in the roentgenogram). (B) After six weeks treatment with streptomycin HCL, the infiltrations show conglomeration; during this period the oropharyngeal ulcers healed. (C) Two months after discontinuation of crystalline streptomycin treatment (in all, he received 254 Gm. in 5 months), complete clearance of infiltrations; a few calcific apical foci are seen. Sputum negative on concentrate and culture. A follow-up examination six months after discontinuation of treatment revealed disease arrested.

given for an additional two and a half months (140 gm.). In all, she received 210 gm. Considerable improvement resulted in spite of the fact that the tubercle bacilli in the sputum had been found resistant to streptomycin early in the course of treatment.

In the remaining three patients no appreciable effects were noted from the second course of treatment although in one tuberculous bronchitis improved. In a woman of 23 years with exudative productive tuberculosis and a large cavity in the right lower lobe complicated by tuberculous bronchitis and laryngitis, treatment with noncrystalline streptomycin (1-2 gm. for 3 months, 174 gm. total) was followed by inhalation of crystalline streptomycin (0.5 gm. daily, 23 gm. total). The condition improved sufficiently to allow performance of cavernostomy. The rating of this group of patients, treated with crystalline streptomycin after having received other forms of streptomycin, was V.G., three; G., three; and U., five. It is noteworthy that these 11 patients were treated with streptomycin, in one form or another, on an average of four and a half months and in only three were the toxic effects marked.

Toxic Reactions

In approximately 25 per cent of the patients treated with crystalline streptomycin there were no significant side reactions except for slight dizziness after the second or third week of treatment which disappeared spontaneously. However, in only a few were there no side effects at all. In approximately 50 per cent there developed persistent dizziness, dermatitis, occasionally vomiting and headache. The symptoms were of moderate intensity and did not interfere with the administration of the streptomycin. In the remaining 25 per cent the reactions were severe, occasionally caused interruption and, in a few, discontinuance of treatment. In none were serious complications met in the way of deafness, impaired vision or renal failure.

It is difficult to get a true picture of the incidence or severity of side reactions in patients with pulmonary tuberculosis treated with streptomycin. The patients are apt to minimize their symptoms for fear that the treatment will be discontinued if they complain of any untoward effects. This was brought out clearly on several occasions when inquiry was made whether a particular patient felt pain after months of intramuscular injections, every four hours, day and night. A few would admit that some nurses gave them "less" pain. It is our impression that crystalline streptomycin causes less pain at the site of injection than the non-crystalline forms. The severest side reactions were encountered in patients of the older age groups.

It is impossible to compare the frequency and severity of side

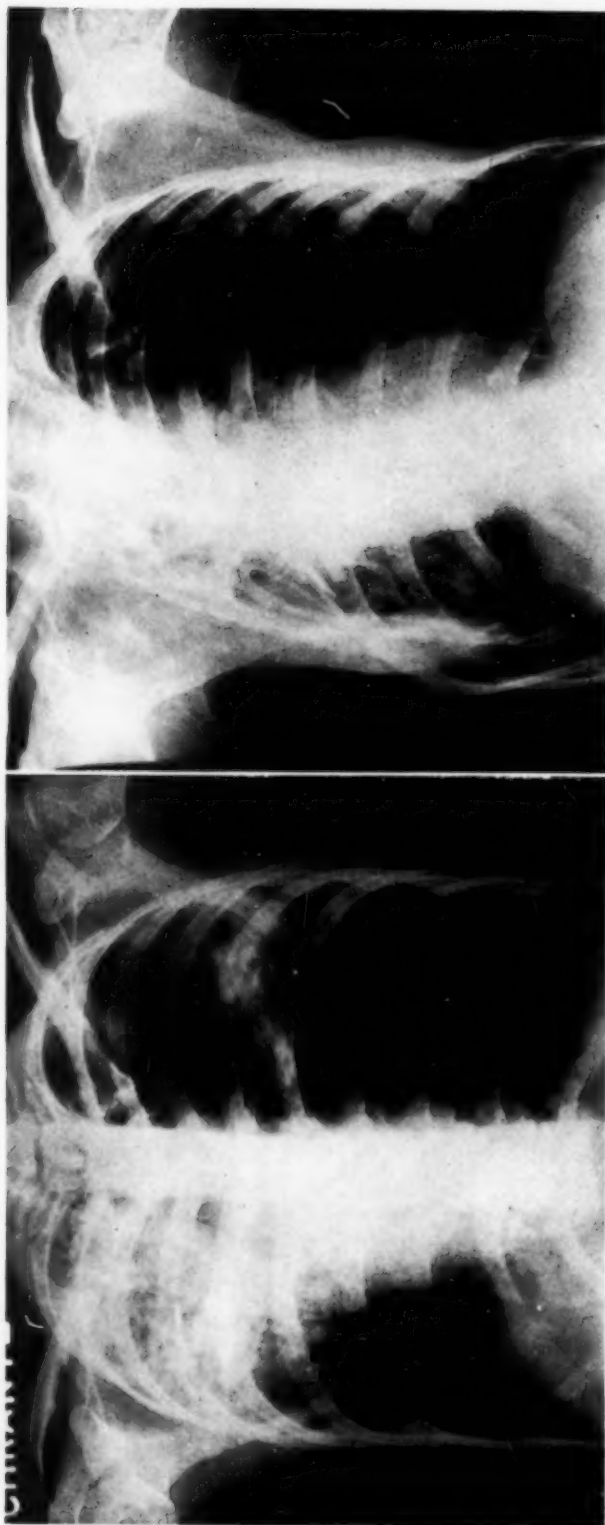


FIGURE 8A

FIGURE 8B

Fig. 8: Streptomycin treatment of advanced tuberculosis with cavitation in a girl of 17, preliminary to possible thoracoplasty. Successful results. (A) Right lung is seat of a caseocavernous tuberculosis; exudative infiltration with evidence of cavitation in left upper lobe. (B) Three-stage, 7-rib thoracoplasty performed toward the end of a course of streptomycin treatment (non-crystalline, 3 Gm. daily for 3 months and, after a two-month interruption, crystalline streptomycin 1 Gm. daily for an additional 2 months; in all, 340 Gm.). Disease apparently arrested; gastric cultures still positive for acid-fast organisms.

reactions in the group treated with crystalline streptomycin with those encountered in the control group. It is our impression that in the latter there were more instances of transient allergic edema and febrile rises in temperature. Asthmatic seizures were encountered in several patients of the control group who had tuberculous laryngitis treated by inhalations of streptomycin. These were associated with edema of the vocal cords. Among the patients treated with crystalline streptomycin by injection, two instances were observed of mild stomatitis and three of ulcerative stomatitis. This condition was encountered only once in mild form in the control group. The allergic nature of the stomatitis was verified by provocative doses of streptomycin after the mouth lesions had cleared.⁴ On the whole, the toxic reactions of crystalline streptomycin were of the same intensity as those encountered with other forms of streptomycin. It should be noted that the patients treated with crystalline streptomycin were of an older age group and received the drug for longer periods of time than the control group. Audiometric and vestibular tests did not give any more information than the gross clinical findings. With few exceptions, eosinophilia was present in the blood in percentages ranging from 10 to 20, in one, as high as 67.

Bacterial Resistance

It is estimated that in 80 per cent of patients with pulmonary tuberculosis treated with streptomycin for four months or longer, the tubercle bacilli acquire resistance to more than 10 mcg. of streptomycin per cc. of culture medium.⁵ Since the effects of streptomycin are most pronounced within the first two months of treatment, the problem arises whether or not the resistance acquired by the tubercle bacilli in vitro is a gauge of the effectiveness of streptomycin in vivo.

Feldman, Karlson and Hinshaw⁶ obtained tubercle bacilli with normal sensitivity to streptomycin from a patient before treatment and, later, from the same individual, a culture resistant to streptomycin in vitro. In concurrent experiments they noted that guinea pigs infected with the streptomycin-sensitive cultures responded favorably to the treatment. However, in three of the 10 animals active lesions of recent origin were present. But streptomycin-resistant tubercle bacilli were obtained from each of the three animals. The disease in the animals infected with the streptomycin-resistant culture failed to yield to treatment. They conclude that infection of guinea pigs induced by tubercle bacilli resistant in vitro to streptomycin are refractory to treatment with this antibiotic.

Our bacteriologic investigations, carried out in cooperation with

the Department of Bacteriology of the College of Physicians and Surgeons, under the supervision of one of the authors (M.M.S.), have not been illuminating. Several patients had resistant organisms in the sputum before streptomycin treatment was begun and did well. Others continued to improve after the organisms had been found resistant to streptomycin. As will be noted in the accompanying table, in a considerable number of patients streptomycin was given for four months or longer, which was ample time for the acquisition of drug resistance by the tubercle bacilli. Yet, such patients are among those who rated high as far as immediate therapeutic effects were concerned. In no instance was a sudden change encountered in the course of the disease that could be ascribed to possible resistance acquired by the tubercle bacilli. It is equally clear, from the results in the U. classification, that streptomycin applied for longer than four months (possibly within a shorter period) does not alter the course of tuberculosis if the tubercle bacillus is not responsive to the antibiotic.

Bacterial resistance plays an important role in the treatment of acute bacterial infections and, most likely, this holds true for tuberculosis. However, in a chronic disease such as tuberculosis, the resistance of the patient is more decisive in determining the eventual outcome than drug-resistance acquired by the tubercle bacilli. Clinical and roentgenographic improvement may take place in the presence, very likely in spite of drug-resistance. The clinical significance of acquired bacterial resistance in the treatment of tuberculosis with streptomycin is an important problem for future investigation.

Suggested Plan of Treatment

On purely speculative grounds the following is suggested: Streptomycin may be found most effective if used in the manner of therapeutic pneumothorax. Both forms of treatment are essentially suppressive; one exerts its effects mechanically, the other biotically. Both aid natural processes of healing. In the treatment of advanced pulmonary tuberculosis, associated with fever, cough and expectoration, when there is imminent danger of canalicular spread of infection, relatively large doses of streptomycin (2 gm. daily, in divided doses) might be used until there is some degree of stabilization of the disease. Less acutely progressive tuberculosis may require 1 gm. daily. The dose of streptomycin might shortly be cut to 0.5 or 1 gm., administered two or three times a week, to maintain a sustained suppressive effect of the antibiotic in the body until the disease shows a decided tendency to regress roentgenologically. The total dosage could be kept within

150 gms., well within toxic limits and possibly within the period in which most of the organisms acquire resistance.

If the disease is amenable to collapse or other surgical measures, and if there is need to fortify the patient with streptomycin because of undue operative risks, the antibiotic should be administered for a short time prior to such contemplated operations and for a time thereafter.

In the present state of knowledge of the value and limitations of streptomycin, it is inadvisable to use the agent as a short-cut in the treatment of pulmonary tuberculosis or, for that matter, as a routine method of treatment under any circumstance. As long as there is a reasonable expectation of obtaining arrest of the disease on a modern sanatorium regimen, streptomycin should be reserved for special indications.

SUMMARY

The immediate effects of crystalline streptomycin were studied in 44 patients with advanced pulmonary tuberculosis. The findings were evaluated in the light of results obtained in 31 patients treated with noncrystalline streptomycin, and in 11 patients treated with both forms. Viewed against a background of experience in the treatment of similar types of patients by conventional methods, it was found that:

1) Crystalline streptomycin was associated with notable degrees of roentgenographic regression of the disease in approximately 60 per cent of patients with acute exudative, or recent caseo-cavernous tuberculosis. In a few it was associated with apparent arrest of the disease. The improvement was at a pace and to a degree seldom seen in similar types of patients treated on a rest regimen alone. In the remainder, the roentgenographic changes were rarely progressive under streptomycin treatment. They were either stationary or slightly regressive. Significant to marked symptomatic improvement occurred in the majority as evidenced in a decline of fever, decreased cough and expectoration, increased weight and improved well-being.

2) Crystalline streptomycin was found to have no demonstrable effect on long-standing fibrocavernous tuberculosis. The potential toxic effects of streptomycin, particularly in older age groups, counterbalances any temporary improvement which may be derived from the use of the agent in this type of disease.

3) Streptomycin was effective in the treatment of tuberculous laryngitis and bronchitis. Draining fistulas closed promptly, but occasionally reopened. It was of doubtful value in the treatment of chronic tuberculous empyemas, excepting possibly preoperatively.

4) Streptomycin was found most valuable in conjunction with

collapse and other surgical measures. In occasional instances it made surgical intervention unnecessary. Often it broadened the field of application of surgical treatment by rendering previously inoperable cases amenable to surgery.

5) In the relatively small number of patients studied, no demonstrable differences could be detected in the immediate therapeutic effects in those treated with crystalline streptomycin as compared to those treated with the noncrystalline forms. It should be noted that the groups of patients in which the comparison was attempted were not treated simultaneously. Furthermore the patients treated with crystalline streptomycin had, by and large, more advanced tuberculosis often associated with serious complications.

6) The toxic effects of crystalline streptomycin were, with few exceptions, not of a severity to cause abandonment of the treatment. Short interruptions were necessary in many instances. Crystalline streptomycin appeared to cause less pain at the site of injection and was less often associated with febrile reactions than the noncrystalline forms. However, stomatitis was more common with the former. Dizziness and allergic skin manifestations occurred with approximately the same frequency and intensity.

7) The optimum daily and total dosages and the best manner of applying streptomycin were not established in this study.

RESUMEN

Los efectos inmediatos de la estreptomicina cristalina se estudiaron en 44 enfermos con tuberculosis pulmonar avanzada. Sus hallazgos fueron evaluados a la luz de los resultados obtenidos en 31 enfermos tratados con estreptomicina no cristalina y en 11 enfermos tratados con ambas formas.

Comparando con la experiencia anterior del tratamiento de enfermos similares por los métodos habituales, se encontró que:

1) La estreptomicina cristalina fué asociada con notables grados de mejoría radiográfica de la enfermedad, aproximadamente en 60 por ciento de enfermos con tuberculosis aguda exudativa o caseo-cavernosa reciente. En unos pocos fué asociada con aparente detención de la enfermedad. La mejoría fué con un ritmo y con un grado raras veces visto en tipos similares de enfermos tratados bajo el régimen de reposo solo. En los demás los cambios radiográficos fueron rara vez progresivos bajo el tratamiento de la estreptomicina. Estos eran ya sea estacionarios o ligeramente regresivos. Un grado de mejoría sintomática marcada o evidente fué notado en la mayoría, como lo mostraba la declinación de la fiebre, la disminución de la tos y la expectoración, aumento de peso y mejoría del bienestar.

2) La estreptomycinina cristalina se encontró que no tenía efecto demostrable en la tuberculosis fibro cavernosa de larga duración. El potencial de efectos tóxicos de la estreptomycinina especialmente en los grupos de mayor edad, contrabalancea cualquier mejoría temporal que puede derivarse del uso del agente en esta clase de enfermedad.

3) La estreptomycinina fué efectiva en el tratamiento de la tuberculosis laringea y bronquial. Las fístulas supurantes se cerraron prontamente, pero a veces se volvían a abrir. Es dudoso el valor del tratamiento de la estreptomycinina en los empiemas crónicos tuberculosos, con excepción probablemente de su uso preoperatorio.

4) La estreptomycinina se encontró más valiosa agregándose al colapso y a otras medidas quirúrgicas. En casos ocasionales, hace la intervención quirúrgica innecesaria. A menudo amplía el campo de aplicación en el tratamiento quirúrgico, volviendo los casos antes inoperables susceptibles de someterse a la cirugía.

5) En el pequeño número relativamente de enfermos estudiados, no se encontraron diferencias demostrables que puedan ser aclaradas por los efectos inmediatos terapéuticos entre aquellos tratados con estreptomycinina cristalina, comparados con los tratados con las formas no cristalinas. Debe notarse que los grupos de enfermos en los que la comparación fué intentada no fueron tratados simultáneamente. Es más, los enfermos tratados con estreptomycinina cristalina, tienen con mucho formas más avanzadas de tuberculosis a menudo asociadas con complicaciones serias.

6) Los efectos tóxicos de la estreptomycinina cristalina, fueron con pocas excepciones no de una severidad como para causar la suspensión del tratamiento. Se necesitaron cortas interrupciones en muchos casos. La estreptomycinina cristalina pareció causar menos dolor en el punto de la inyección y menos a menudo se asoció con reacciones febriles que en las formas no cristalinas. Sin embargo, las estomatitis fueron más comunes con la primera.

7) Los mareos y las manifestaciones alérgicas cutáneas, ocurrieron aproximadamente con la misma frecuencia e intensidad. La dosis óptima diaria y la mejor manera de aplicarse de la estreptomycinina, no se establecieron en este estudio.

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A D D E N D U M

The forementioned plan of treatment was applied to a group of 34 patients at the Morrisania City Hospital. Dr. Herbert Katzev and one of the authors (E.H.R.) supervised the management of these patients. These were mostly Negroes and Porto Ricans with caseocavernous or bilateral exudative tuberculosis. Streptomycin and, more recently, dihydrostreptomycin, was given intramuscularly in 0.5 gm. doses, twice daily. In patients with hyperacute disease, a full gm. was injected twice daily. At the end of two weeks daily treatment, an x-ray of the chest was taken. If the disease showed a tendency to improve and the symptoms were in keeping, streptomycin was administered in 1 gm. doses every second or third day, depending on individual needs. If no improvement was noted, the daily schedule was maintained. By the end of three or four weeks of daily treatment most patients were ready for an interrupted schedule. During the period of streptomycin administration, every effort was made to incorporate some form of collapse treatment.

It is our impression that an interrupted schedule of applying streptomycin is not followed by as dramatic immediate results as that following daily use of the antibiotic, especially when given in 2 gm. daily doses. But inasmuch as in the types of patients treated one is primarily concerned with the "long pull" effect of the antibiotic, the results are sufficiently encouraging to warrant an extended trial of this plan of treatment. Recent reports by Vern F. Deyke and his associates (*Ann. Int. Med.*, 30:619, 1949), Emil Bogen (*Med. Clin. N. A.*, March 1949) and W. L. Howard and his associates (*Am. Rev. Tuberc.*, 59:391, 1949) on certain advantages in the use of single 1 gm. daily injections, on an interrupted schedule, lend support to the belief that the administration of streptomycin, to be most effective in the treatment of advanced pulmonary tuberculosis, should be stretched over a period of months, not weeks. Less advanced disease requires correspondingly shorter periods of treatment. The final outcome depends on natural processes of healing which patients possess to varying degrees.

Calcified Splenic Cyst

Report of a Case*

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Splenic cysts, in general, are infrequently encountered in medical practice. Among these, calcified cysts are extremely rare. Harmer and Chalmers,¹ in a review of the literature to 1946, reported a total of 163 splenic cysts of all types. Our comprehensive review of medical publications revealed only 31 cases of calcified splenic cyst on record to date: Fowler² reported 7 cases; Foldes,³ Gatersleben,⁴ Baumann and Kohnstamm,⁵ Segelman,⁶ Scotson,⁷ Arenas and Gonl,⁸ Goinard,⁹ Schawan,¹⁰ Dellannoy et al,¹¹ Romano et al,¹² Bachman,¹³ Zdansky,¹⁴ Nosiglia,¹⁵ Elkeles and James,¹⁶ Gallagher and Mossberger,¹⁷ Culver et al,¹⁸ Snoke,¹⁹ Neidhart,²⁰ Duggan,²¹ and Jameson and Smith²² reported one each; Kierluf²³ reported four additional cases.

We are presenting what we believe to be the thirty-second reported instance of this clinical finding.

Many of the calcified splenic cysts have been discovered as a result of investigation of pressure symptoms of an expanding lesion in the left upper quadrant. Frequently, a history of parasitic infestation or of localized trauma called attention to possible splenic pathology. Exploratory laparotomy, as a rule, established the correct diagnosis. Some of the cases have been observed as incidental findings on radiologic examination and the etiologic background investigated in retrospect. Many of these, as in the case we are citing, yielded no etiologic clues.

REPORT OF CASE

The patient, P. J., a 51 year old white male was first admitted to our hospital on August 12, 1946, complaining of shortness of breath and wheezing of many years duration.

The patient was born on a farm in Illinois on September 28, 1895. He lived on this farm until June 26, 1918 when he entered the U. S. Army. He served within the continental limits of the United States, except for two days in England and five months in France, and was discharged on May 19, 1919. After discharge, he drove a truck in Wisconsin and Illinois from 1919 until 1932. He was a blacksmith for ten years in Beloit, Wis-

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consin, a bartender for the next two years, followed by odd jobs for the ensuing two years. He never left that community.

The patient had measles, mumps, and scarlet fever in childhood. There were no known complications. In the winter of 1918 and 1919, while in France, he was hospitalized four months for "rheumatism," manifested by painful swellings of the feet, knees, shoulders, and hips, with residual stiffness in these joints. There were no definite findings referable to the heart. In 1944 he again developed some swelling and pain of both knees and the left elbow, which lasted six weeks. He was treated, symptomatically, at home and made an uneventful recovery.

Since the age of 33 (1929), the patient has been suffering from seasonal bronchial asthma.

He was studied from the allergic standpoint and the significant positive findings were an eosinophilia of 11 per cent and skin sensitivity to dog dander, cat dander, cow dander, rabbit dander, sheep wool, chicken feathers, duck feathers, goose feathers, orris root, and flax seed. He was discharged September 19, 1946, with diagnoses of (1) allergic bronchial asthma, chronic, with secondary pulmonary emphysema, and (2) chronic arthritis, type undetermined.

The patient was at home for six weeks, when he suddenly developed severe dyspnea associated with mild shock. An x-ray of the chest was taken at another hospital, and the diagnosis of a right spontaneous pneumothorax was established. He was kept in bed for ten days under supportive management, and transferred to our hospital on November 5, 1946, for further care.

On the second admission, the patient appeared well developed, poorly nourished, slightly dyspnoeic while sitting up, and chronically ill. There were non-tender, shotty cervical nodes bilaterally. The trachea deviated somewhat to the left. The chest was emphysematous, with diminished excursions bilaterally. There was increased resonance throughout the right hemithorax, particularly in its upper half. There were no adventi-

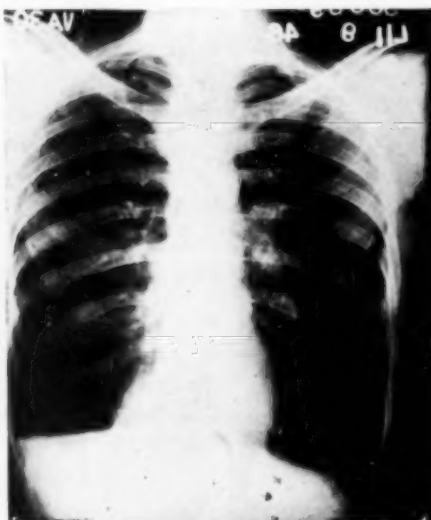


FIGURE 1

Fig. 1: Postero-anterior teleoroentgenogram of the chest.



FIGURE 2

Fig. 2: Left lateral view of lower chest and upper abdomen.

tious sounds. The blood pressure was 138/72. The heart sounds were distant but the heart was otherwise normal. The abdomen was scaphoid with no tenderness, masses, or scars. Rectal examination was normal. There was moderate clubbing of the fingers. The skin was clear. Clinical course was afebrile.

Routine laboratory studies revealed a normal blood count and differential smear, normal urinalysis and negative serologic test for syphilis. A chest x-ray taken on November 9, 1946 revealed bilateral basal emphysema, moderate degree of interstitial fibrosis, and residual 20 per cent pneumothorax on the right with a small amount of fluid at the right base. A peculiar round, ring-like, radio-opaque shadow was noted under the left hemidiaphragm, which was first considered as an artifact because of its almost perfect ring appearance and location in a relatively unimportant portion of a 14 x 17 inch film of the chest. The presence of this ring shadow on subsequent chest films led to further investigation (Fig. 1).

Since the patient presented no symptoms of an abdominal nature and since the calcification of the suspected lesion attested to its age and suggested inactivity, there were no definite indications for exploratory laparotomy, even though clinical curiosity was a strong factor. We then decided to attempt to establish the nature of the Roentgen shadow and its specific location by elimination studies.

Lateral film of the lower chest and upper abdomen placed the shadow posteriorly and confirmed its spheroidal contour (Fig. 2). A Bucky film of the abdomen suggested splenic location (Fig. 3), but was not sufficiently diagnostic. A lateral view of the barium-filled stomach (Fig. 4) and barium enema study (Fig. 5) placed the lesion outside of the gastro-intestinal tract. Intravenous urograms separated the ring shadow from the kidney mass (Fig. 6). Diagnostic pneumoperitoneum (Figs. 7 and 8) localized the calcified spheroidal cyst within the clearly outlined splenic shadow. The diagnosis of asymptomatic calcified splenic cyst was then made on the basis of the above, indirect observations.

Careful search was then made for possible etiological clues as to the formation of the cyst. Clinical history was non-contributory. Blood chemistry studies revealed an NPN of 30 mgm. per cent, a blood sugar of 94 mgm. per cent, a total serum protein of 6.8 mgm. per cent with albumin 5.1 mgm. per cent and globulin 1.7 mgm. per cent. The alkaline phosphatase and acid phosphatase were 5.4 and 1.2 Bodansky units, respectively. The serum cephalin-cholesterol flocculation test was negative.

Hematologic studies were normal. The blood count and differential smear were normal. Bleeding time and coagulation time were 2 minutes, and 4 minutes, respectively. Sternal marrow smear was normal. Clot retraction was complete in two hours. The platelet count was 190,000 per c.m., and the reticulocyte count was 1.4 per cent. The sedimentation rate was 8 mm. per hour (Westergren). Hematocrit was 46, and the erythrocytic fragility began hemolysis at 0.44 per cent Na Cl, and completed hemolysis at 0.34 per cent Na Cl. (Control: beginning hemolysis at 0.44 per cent Na Cl and complete hemolysis at 0.34 per cent Na Cl.).

Repeated sputa on concentrate and plain smear were negative for acid fast bacilli, and a culture of a gastric aspiration was negative for acid-fast bacilli.

The echinococcus skin and complement-fixation tests were both neg-

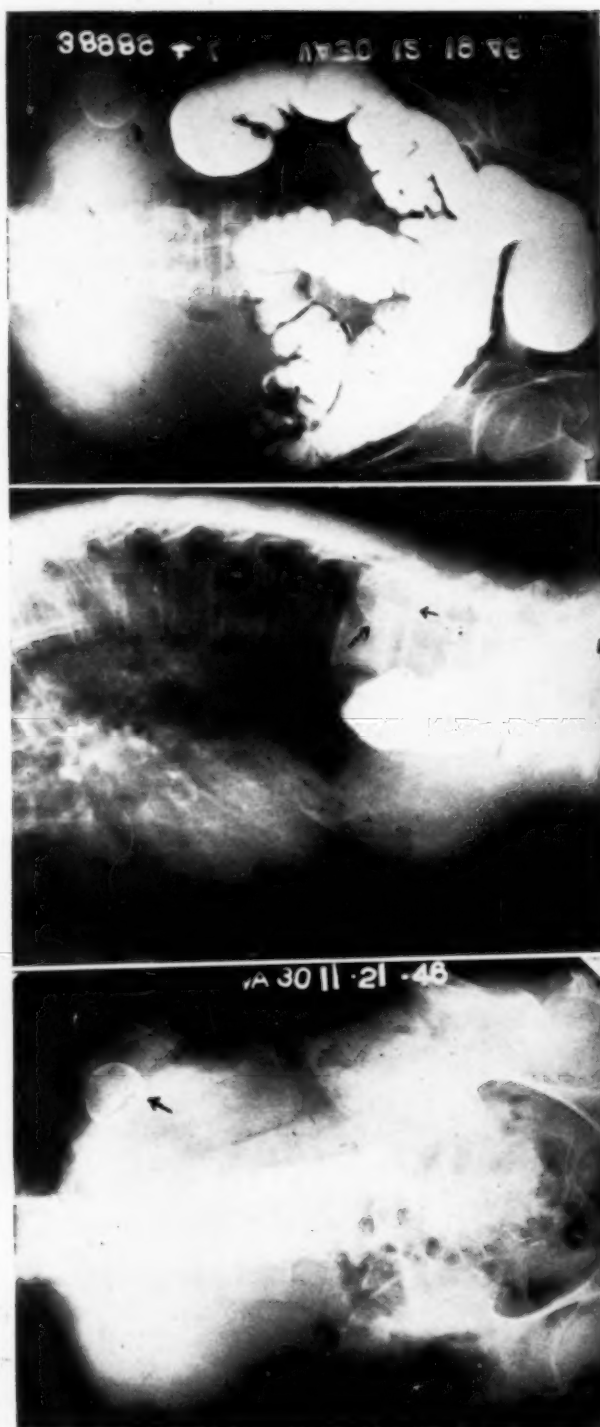


FIGURE 3

FIGURE 4

FIGURE 5

Fig. 3: Bucky film of abdomen.—Fig. 4: Lateral view with barium billed stomach.—Fig. 5: Barium enema.

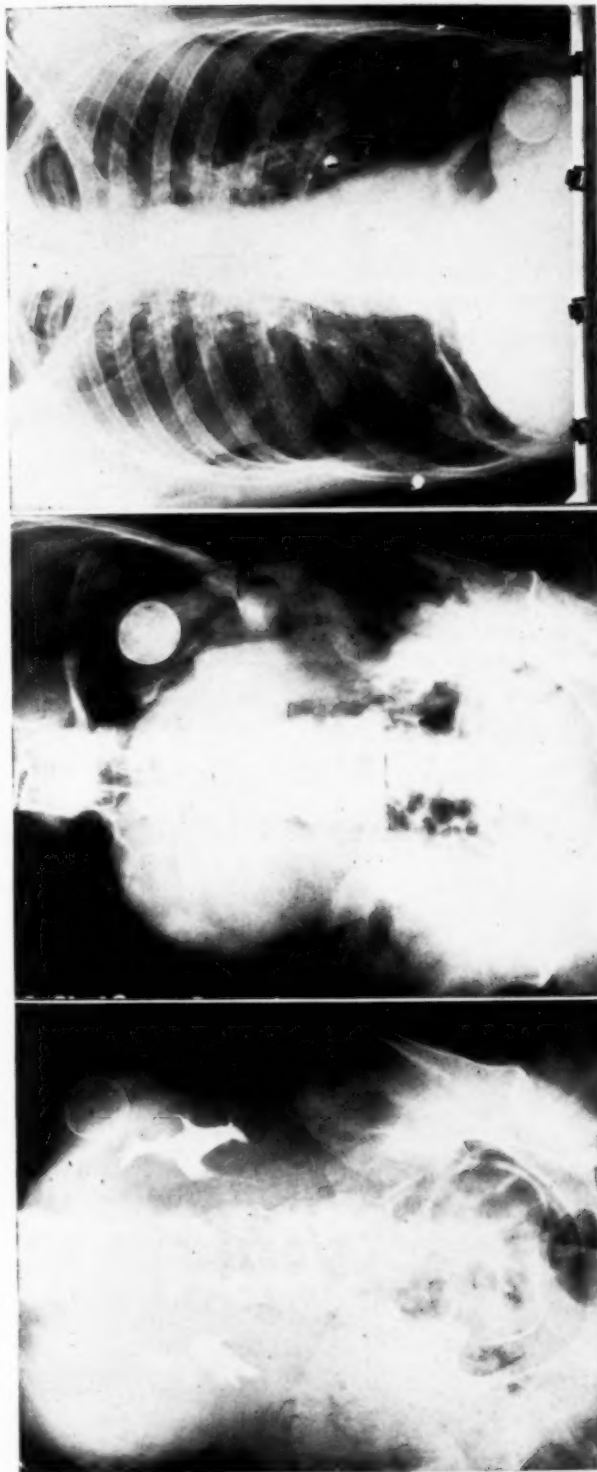


FIGURE 6

FIGURE 7

FIGURE 8

Fig. 6: Intravenous pyelogram.—Fig. 7: Abdomen after diagnostic pneumo-peritoneum.—Fig. 8: Postero - anterior teleoroentgenogram of the chest after diagnostic pneumo-peritoneum.

ative. Thick and thin blood films failed to reveal the presence of malarial parasites.

An electrocardiogram was within normal limits.

The patient made an uneventful recovery from the spontaneous pneumothorax and the bronchial asthma was controlled. There remained a total lack of symptomatology referable to the abdomen, and the patient was discharged on February 17, 1947.

SUMMARY

A case report of an asymptomatic calcified splenic cyst is presented as an addition to the 31 cases previously recorded in the literature. The diagnosis was made by Roentgen elimination studies, initiated by the observation of an unexpected subdiaphragmatic shadow on a teleroentgenogram of the chest. No etiologic background could be established.

RESUMEN

Se presenta un informe de un caso asintomático de quiste calcificado del bazo, como adición a los 31 casos sobre los que se había informado previamente en la literatura. Se hizo el diagnóstico mediante estudios roentgenológicos eliminativos, iniciados por la observación de una sombra subdiafragmática inesperada en el teleroentgenograma torácico. No se pudo establecer la etiología.

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The Surgical Lesions of Pulmonary Coccidioidomycosis*

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Coccidioidomycosis is a highly infectious disease caused by the diphasic fungus *Coccidioides immitis*. It occurs in a primary form, which is an acute benign respiratory infection; and in a progressive form, which is characterized by wide-spread dissemination to the skin, subcutaneous tissues, viscera, bone and other tissues.

The disease is largely confined to endemic areas in the desert regions of Arizona, New Mexico, West Texas and in the great Central Valley of California. These areas have a dry, dusty climate and the incidence of acute infections is at its peak in the dry seasons.¹ Most of the cases of coccidioidomycosis in the United States which have been reported in the literature have either resided in or have visited one of these areas.

Pulmonary infection occurs through the inhalation of the mycelial form of *Coccidioides immitis* which is in all probability borne by the dust in the endemic areas.² The spherules, the form commonly seen in infected tissue, can be infective, but they are not important epidemiologically.

The incubation period is eight to twenty-one days.³ The onset of symptoms resembles that of an upper respiratory infection with fever, chest pain, productive cough and sore throat.^{4,5} The majority of infected persons never see a physician and most patients who are hospitalized in the acute stage of the disease seek medical attention only because they have chest pain, hemoptysis or severe malaise.

Characteristically these symptoms subside in from one to two weeks and the patient is left with a marked immunity to future exogenous or endogenous reinfection.

Dissemination occurs in only about one per cent of the primary infections which are severe enough to bring the patient to a physician. If it does occur, there is usually some evidence of progression within the first few weeks after the initial infection; the initial symptoms becoming progressively worse with fever, weakness and weight loss predominating. The most common sites

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of dissemination are the lungs, lymph nodes, skin, viscera and bones. About half of the cases with disseminated disease terminate fatally.⁶

The most common complication of pulmonary coccidioidomycosis is the formation of a cavity. This occurs in approximately four to six per cent of the acute cases which are severe enough to cause the patients to seek medical attention.^{4,5} The cavitation persists after the acute phase of the disease has passed and characteristically is asymptomatic. The majority of the cavities close in from three to six months if activity is curtailed. Even if the cavity remains patent the patient may return to normal activity without ill effects and the cavity will eventually close in most cases.⁷ Occasionally hemoptysis develops, but this is usually minimal and has been treated successfully by pneumothorax,⁸ although this form of treatment is of little value in promoting cavity closure. Surgery is rarely indicated in these cases and only a few operations have been reported in the literature. Peers, Holman and Smith⁹ have reported a case in which they performed a right upper lobectomy because of their fear of a dissemination of the disease in a twenty-five year old white female. Following the lobectomy, she developed a bronchopleural fistula and an empyema from which *Coccidioides immitis* was isolated. Despite this complication there was no evidence of dissemination and the patient recovered following a thoracoplasty. Quill and Burch¹⁰ call attention to a lobectomy performed by Blades because of a persistent hemoptysis in a patient with a residual cavity.

We are reporting ten cases of primary pulmonary coccidioidomycosis which had had unusual complications for which surgery was indicated. Residual cavitation was shown to be the source of difficulty in eight of these cases, while one had an undiagnosed solid tumor and another had a spontaneous pneumothorax with *Coccidioides immitis* in the pleural effusion. In all, six lobectomies and four decortications were performed. Since all these cases were unusual, a clinical abstract will be given on each.

CASE REPORTS

Case 1: This 25 year old white male was born in Riverside, California. He was stationed at Williams Field in a desert area of Arizona from February 1940 to July 1941. Six months after arrival at Williams Field there was a chronic cough productive of one tablespoonful of mucoid sputum daily which was frequently blood tinged. Although the sputum continued to be blood tinged he did not report to a hospital until early in 1943, when there was severe pain in the right anterior chest. X-ray examination showed a thin-walled cavity in the right mid-lung field. He was transferred to Fitzsimons General Hospital in April 1943 at which time a coccidioidin skin test was positive, complement fixation for coccidioides was positive, and *Coccidioides immitis* was cultured from the

sputum. The sputum was negative for tuberculous organisms. He was retired from the Army in December 1943. On attempting to return to work as a draftsman, he felt weak, tired easily and continued to have a cough productive of blood tinged sputum. There was a weight loss of eleven pounds and on ten occasions during the twenty months there were gross hemoptyses of from one to five mouthfuls of bright red blood. The pain continued in the right chest and he returned to the hospital in September 1945. At this time, x-ray films showed the persistence of a 4 x 10 cm. cavity in the right lower lobe and it was decided that his symptoms warranted a lobectomy. At the time of thoracotomy, October 4, 1945 the cavity was found to cross the intralobar fissure so as to involve the posterior inferior portion of the right upper lobe as well as the entire dorsal division of the right lower lobe. The right lower lobe and a small portion of the right upper lobe were resected. Upon gross examination of the cavity following removal, large numbers of amorphous gray bodies varying in size from 1 to 1.5 cm. were seen lying free in the cavity. These were found to be composed of mycelia and spores. On the prepared slides a search for coccidioides spherules was unsuccessful. However, small fragments of septate mycelia with chlamydospores were seen and smears taken from the cavity contained large numbers of spherules and mycelia. *Coccidioides immitis* was recovered on culture from smears taken from the cavity. There was an uneventful postoperative course and the remainder of the lung expanded to fill the chest cavity. On a postoperative check-up two months following surgery, he was free from his major symptoms.

The indications for surgery in this case were persistence of cavitation, marked ease of fatigue, hemoptysis, chest pain, weight loss and productive cough over a two and one-half year period.

Case 2: This 22 year old white male was born in Los Angeles, California and spent the months of August, September and October 1943 on maneuvers in the desert near Yuma, Arizona and in Southern California. While on these maneuvers, severe pain developed in the left anterior chest which was made worse on deep inspiration and coughing. He was hospitalized and told that there was a large cavity in the left lung field. A coccidioidin skin test was made at that time and was markedly positive. He was returned to general duty in two and one-half months although he was not informed as to whether or not the cavity was closed. There were episodes of pleuritis pain on the left side which occurred at monthly intervals and lasted from seven to eight days. In August 1945, while on Guam, he was hospitalized because of general weakness, malaise and fever. X-ray films showed an area of density 4 cm. in diameter in the left mid-lung field and he was returned to the Zone of the Interior. Two months later there was very little disease seen on x-ray examination. On an x-ray film taken December 20, 1945 a large thin-walled cavity was seen in the superior portion of the left lower lobe and this cavity was seen in all subsequent films, although it varied considerably in size. The sputum was positive for *Coccidioides immitis* and coccidioidin skin test was positive in one to one hundred dilution. Blood was sent to Dr. Charles Smith at Stanford University for serological examination and the complement fixation was found to be positive but of low titre, indicating that the disease was well controlled. Repeated sputum examinations were negative for acid-fast bacilli. After almost a year of hospitalization, the symptoms of weakness, malaise, fever and chest pain

persisted and it was decided that lobectomy should be performed. The left lower lobe was removed on July 25, 1946. On cut section the cavity was empty except for a few cc. of thin grayish-yellow fluid. Smears from this fluid revealed mycelia and cultures were positive for *Coccidioides immitis*. Neither form of the fungus was seen on the prepared slides of the cavity wall. There was an active process in the lower portion of the lobe with extensive bronchitis, bronchiolar pneumonia, and interstitial pneumonitis. Following the operation there was x-ray evidence of scattered soft lesions throughout the right lung field. It was feared that this might indicate a dissemination of the disease and blood was again sent to Dr. C. E. Smith for serological examination. However, this examination showed no evidence of a coccidioidal infection. The lesion in the contralateral lung cleared progressively and within two months this lung field appeared completely normal. The remaining lobe expanded completely to fill the left hemithorax. Check-up examination two months following surgery revealed him to be completely free of major symptoms.

Indications for surgery in this case were persistence of a large cavity, chest pain, weakness, malaise and fever.

Case 3: This 25 year old white male was born in New York City. He was stationed in El Paso, Texas from October 1942 until January 1943. A chest x-ray film taken in February 1943 was reported to be negative. He was then transferred to desert areas of California for desert training and remained there until September 1943. One month after leaving the desert training site, he developed a slight productive cough. In February 1944 there was gross hemoptysis which lasted nearly thirty minutes and a chest x-ray film taken at that time was reported as negative. There was continued blood tinged sputum intermittently until August 1944 when the patient coughed up nearly a half cup of blood. Another chest x-ray film was taken, this was again reported as negative. While serving in the E. T. O. in March 1944, he received a compound, comminuted fracture of the left forearm. Throughout this hospitalization there was continued blood tinged sputum. There was weight loss, lassitude, and ease of fatigue. A chest x-ray film taken in December 1945 showed cavitation in the right lung. Tuberculin tests were negative on first and second strength and repeated sputums and gastric analyses were negative for acid-fast bacilli. *Coccidioides immitis* was isolated from the sputum in February 1946 and at this time a coccidioidin test was markedly positive in one to one hundred dilution. At this time, blood was sent to Dr. Charles Smith at Stanford University for serologic tests for coccidioidal infection. The complement fixation titre was positive, 1:8. He was admitted to Fitzsimons General Hospital on September 28, 1946. A bronchoscopy was performed which showed no abnormality except for a small amount of blood tinged sputum which seemed to originate from the right upper lobe bronchus. The symptoms of weakness and ease of fatigue continued. The x-ray appearance of the cavity was unchanged. It was decided that the symptoms warranted a lobectomy and the right upper lobe was removed on October 31, 1946. Grossly, the cavity lining was irregular and caseous and the stump of a broken vessel projected into the lumen. There was only a slight amount of fluid present within the cavity and this contained many spherules of *Coccidioides immitis*. No mycelial forms were seen. Spherules were also seen sparsely placed about the cavity on the prepared slides. Collections of small granulomata were scattered outside of the cavity and these also contained spherules. The postopera-

tive course was uneventful. The remaining lung expanded to fill the right hemithorax and the patient was discharged from the hospital four months after surgery. Within a few days after discharge, he had hemoptyses on two occasions and began to feel ill again. There was a weight loss of ten pounds in the next month and he was re-hospitalized. The sputum was strongly positive for acid-fast bacilli. A small cavity was found within the remaining portion of the right lung. In June 1947 he is still hospitalized for the management of the tuberculous infection.

The indications for surgery in this case were persistent cavity, symptoms of weakness, ease of fatigue and hemoptysis.

Case 4: This 24 year old white male was born in Minnesota. He was stationed at Marana Air Field in Arizona from October 1943 to January 1944 and at Union Field, Arizona during March 1944. In March 1945, he developed a dry nonproductive cough and in May 1945 first noticed blood tinged sputum. In July 1945, while overseas, there was a gross hemoptysis and he was hospitalized. At that time, there was a ten-pound weight loss, ease of fatigue and weakness. X-ray film revealed a cavity in the right upper lung field measuring 1.5 x 2.5 cm. He was transferred to the Zone of the Interior and arrived at Fitzsimons General Hospital on August 20, 1945. At that time, there was no more hemoptysis but a chronic nonproductive cough and the symptoms of weakness and ease of fatigue continued. His sputum was repeatedly positive for *Coccidioides immitis* and repeatedly negative for acid-fast bacilli. He was transferred to another hospital in October 1945 where he continued to run a slight elevation of temperature. The sputum again became blood tinged and there were gross hemoptyses on three occasions during the next four months. He was transferred back to Fitzsimons General Hospital on February 27, 1946. At this time the cavity remained unchanged. Blood was sent to Dr. Charles Smith for serological examination and the report was returned that the complement fixation test was positive for coccidioidomycosis but was of a low titre indicating that the process was well localized. A coccidioidin test was negative one to one hundred but

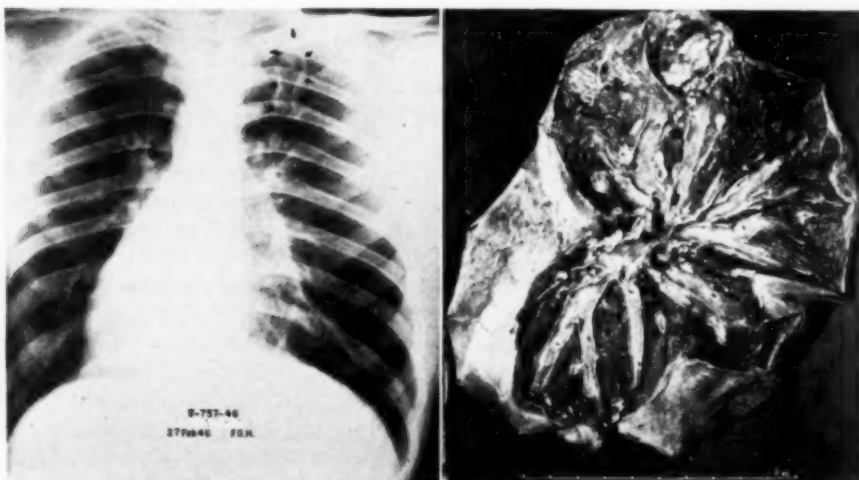


FIGURE 1

PLATE I

FIGURE 2

Fig. 1: Cavitation in right lung field.—*Fig. 2:* Gross specimen showing cavitation.

positive one to ten. Because of the persistence of the severe symptoms after nine months hospitalization, a lobectomy was advised. The right upper lobe was removed on April 22, 1946. Grossly, the cavity was irregular and was lined with both ciliated cylindrical and squamous metaplasia of epithelium. Areas of bleeding granulation tissue were seen. Direct smears from the cavity showed mycelial forms with chlamydospores but no spherules. However, on the prepared slide of the cavity, occasional spherules were seen in the tissue about the cavity. The remaining lobes expanded to fill the entire right thoracic cage. He was seen at a check-up examination two months following surgery. At that time, there was a weight gain of ten pounds and there were no major symptoms.

The indications for surgery in this case were persistent cavitation, weakness, ease of fatigue, low grade fever and hemoptysis over a nine month period. (See Plate I, Figures 1 and 2).

Case 5: This 24 year old white male was born in Illinois. During the summer and fall of 1943, he was on Army maneuvers in the California desert. Following this, there was a chronic nonproductive cough but no symptoms which warranted seeing a physician. He was hospitalized following a routine chest film taken at a Separation Center on November 2, 1945. This x-ray film showed a large fluid-filled cavity in the left upper lobe measuring 6 cm. in diameter and a small round circumscribed density in the right lower lobe measuring 2 cm. in diameter. He was unaware of any primary infection of *Coccidioides immitis*. The physical examination was essentially negative. Smears and cultures of the sputum and gastric contents were repeatedly negative for acid-fast bacilli, although the tuberculin was positive on the second strength. The coccidioidin skin test was negative one to one hundred but positive on one

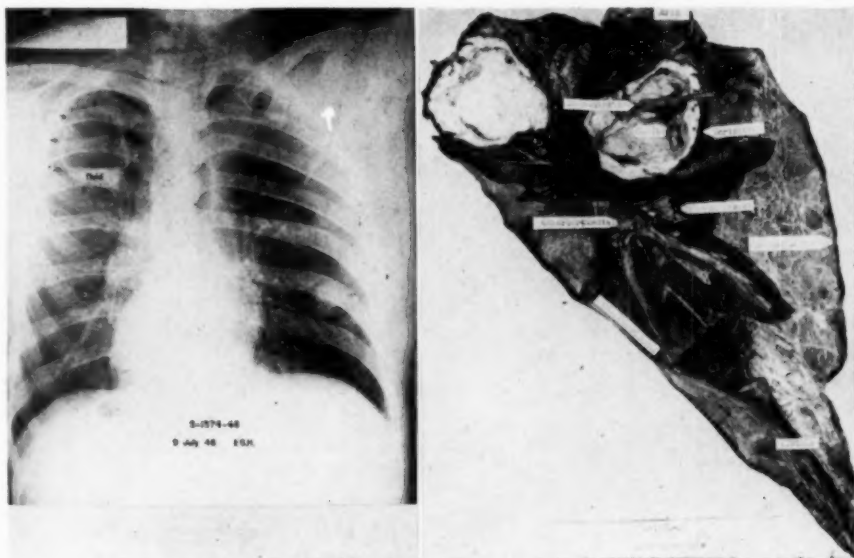


FIGURE 3

PLATE I

FIGURE 4

Fig. 3: Cavity with fluid level, left upper lobe; circumscribed lesion, right lower lobe.—Fig. 4: Gross specimen showing left upper lobe cavity.

PLATE II

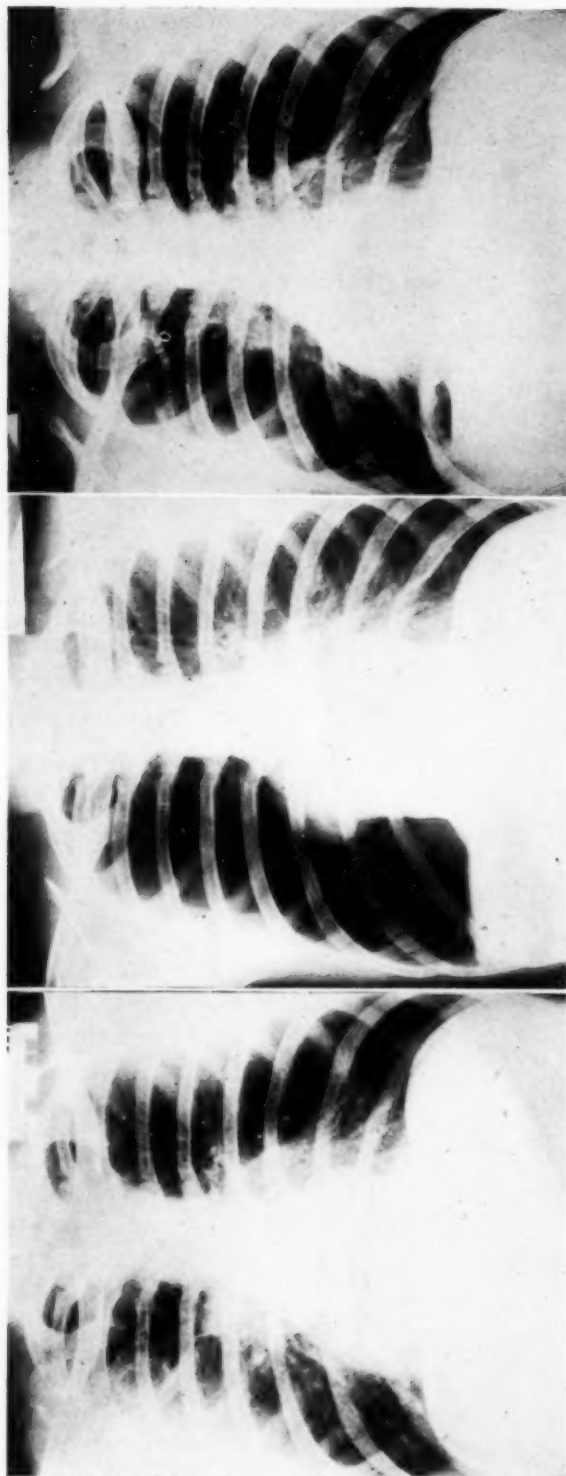


FIGURE 1

FIGURE 2

FIGURE 3

Fig. 1: Cavitation in left upper lung field.—Fig. 2: Spontaneous Pneumothorax with inexpandible lung.—Fig. 3: Following Decortication and segmental resection.

to ten dilution, and *Coccidioides immitis* was recovered from the sputum. In view of the extensive nature of the disease, dissemination was feared and blood was sent to Dr. Charles Smith of Stanford University for serological examination for coccidioidomycosis. The report returned was that there was no evidence of coccidioidomycosis. There was no evidence of change in either of the lesions after ten months hospitalization and, although he was asymptomatic except for a slight cough, it was decided that the large fluid-filled cavity should be removed. A left upper lobectomy was performed on August 12, 1946. On pathological examination of the specimen, no spherule forms of *Coccidioides immitis* were seen but there was an abundance of the mycelial forms which yielded typical colonies on culture. The postoperative course was uneventful and the remaining lung tissue expanded to fill the entire left thoracic cage. He was seen on check-up examination three months following surgery and was free from any significant symptoms.

Indications for surgery in this case were persistent large fluid-filled cavity with contralateral lesion following ten months of observation. (See Plate I, Figures 3 and 4).

Case 6: This 26 year old white male was born in Wisconsin. He was stationed in West Texas during 1942 and 1943. There was no primary illness during this time. He served overseas twenty-two months without difficulty but while on furlough following his return from overseas he began to experience tiredness and ease of fatigue with dyspnea on exertion or active walking. There was blood streaked sputum on several occasions, with occasional bilateral chest pains. Three months later, these symptoms still persisted and in addition there was a sore throat for which he was hospitalized. A chest x-ray film revealed a sharply circumscribed tumor 3 cm. in diameter at the periphery of the left upper lobe. Sputums were repeatedly negative for acid-fast bacilli and a left upper lobe lobectomy was decided upon because of the undiagnosed circumscribed lung tumor. Smears taken from the operative specimen were positive for *Coccidioides immitis* on culture, and the gross and microscopic findings were consistent with a coccidioidoma. Following surgery, the remaining portion of the lung expanded to fill the left hemithorax. Follow-up examinations eighteen months following operation revealed that he still tired easily, but was able to do light work without difficulty.

The indication for surgery in this case was a parenchymal circumscribed solid tumor causing lassitude and chest pain. (See Plate II, Figures 4 and 5).

Case 7: This 25 year old white male was born in Oklahoma. He was stationed at Williams Field, Arizona from March 1942 to December 1942 and in San Joaquin Valley of California from June 1943 to December 1944. He was asymptomatic and was first hospitalized following an x-ray examination taken November 1944 prior to going overseas. This x-ray film showed a cavity in the left upper lung. He was hospitalized immediately and was transferred to Fitzsimons General Hospital in March 1945. At this time, sputum examinations showed *Coccidioides immitis* in great abundance. The cavity failed to close; however, he remained asymptomatic, and was discharged from the service in June 1945. Following his discharge he returned to his home and led an active life until December 4, 1945, when he experienced the sudden onset of pain in the left chest,

spasmodic cough productive of a small amount of whitish sputum, and shortness of breath on the slightest exertion. Two days later he began to feel fluid splashing around in the left chest and had a shaking chill. He returned to the hospital and x-ray examination showed a massive collapse of the left lung with a moderate amount of fluid in the left base. Cultures taken from a specimen of this fluid showed an abundant growth of *Coccidioides immitis*. Aspirations of fluid and air were ineffective in reexpanding the lung and a decortication was performed on January 25, 1946 with a segmental resection of the small cyst wall in the left upper lobe. There was a definite bronchopleural fistula through the cavity. Pathological examination of the cyst wall was inconclusive, but cultures from the cyst were positive for *Coccidioides immitis*. The lung did not completely reexpand following this operation and a second decortication was performed on April 25, 1946. This time the lung was completely expanded but following removal of the intercostal catheter a small air pocket developed in the apex of the lung. The patient preferred to have no further surgery and was discharged from the hospital in June 1946. He has been followed at monthly intervals since this time and is leading an active life, including flying, without symptoms. The small pneumothorax space at the left apex is still apparent.

The indications for surgery were spontaneous pneumothorax with a nonexpansile lung and coccidioidal empyema. (See Plate II, Figures 1, 2 and 3).

Case 8: This 23 year old white male was stationed in a desert area of Arizona from July to October 1942 and at Baker's Field, California from November 1942 to January 1943. He can recall no illness during his residence in either of these areas. He was sent overseas and was wounded in action on April 22, 1945. Routine x-ray examination of a fracture of the right shoulder taken in June 1945 revealed a pulmonary cavity in the apex of the right lung field. Skin tests were made for coccidioidin and tuberculosis and both were reported negative. There was a slight



FIGURE 4

PLATE II

FIGURE 5

Fig. 4: Circumscribed coccidioma, left upper lung field.
Fig. 5: Following resection.

productive cough beginning in September 1945. He was separated from the service in April 1946 because of multiple gunshot wounds. In May 1946 there was an episode of severe pain in the right chest with a cough productive of large amounts of thick grayish sputum and a temperature elevated as high as 105 degrees. He was treated by a physician with penicillin but no x-ray films were taken. The following month, he began to notice a splashing sensation in the right chest and shortness of breath on exertion. A chest x-ray film was taken on August 14, 1946 and revealed a hydropneumothorax on the right with approximately seventy-five per cent collapse of the lung. He was hospitalized at a Veterans' Hospital where a large amount of clear, yellow fluid was aspirated from the chest. The lung expanded until there was only approximately ten per cent collapse and he was transferred to Fitzsimons General Hospital on November 14, 1946. A Mantoux test was positive on first strength but numerous sputum examinations were negative for acid-fast bacilli. A coccidioidin skin test was positive one to one hundred and *Coccidioides immitis* was cultured from the fluid aspirated from the right chest. The lung failed completely to expand despite repeated aspirations and a decortication was performed on January 2, 1947 with wedge resection of the bronchopleural fistula which was at the site of the cavity. No pathological diagnosis could be made of the excised cyst. The operation was followed by complete reexpansion of the left lung. Blood serological examination for coccidioidal infection performed by Dr. Charles Smith of Stanford University both preoperatively on December 26, 1946 and postoperatively on February 18, 1947 gave identical results, with a positive reaction in the complement fixation at one to four dilution and a positive reaction for the precipitins at one to forty dilution. The patient was seen five months postoperatively at which time he had no significant chest symptoms and x-ray film showed the lung well expanded.

Indications for surgery in this case were persistent cavitation with spontaneous pneumothorax, inexorable lung and coccidioidal empyema.

Case 9: This 31 year old white male was born in Rhode Island. He suffered a painful injury to his right chest in a scuffle in the barracks in August 1941 and was hospitalized for two weeks and was then discharged to duty. He received desert training in endemic areas of California from May until December 1943. On one occasion there was pain in the right chest for one day, but aside from that he can recall no symptoms during the stay in the endemic areas. He was asymptomatic until January 1945 when, while on duty in Guam, he developed a productive cough associated with fever, malaise, nausea, vomiting, and pain in the right chest. There was a weight loss of twenty pounds in one month. He was hospitalized on February 26, 1945, and x-ray films taken at that time showed an area of consolidation in the right lower lobe, with circumscribed infiltration in the right apex. Within the next few months, the latter area excavated. He was sent back to the United States by way of Hawaii where numerous sputum examinations were reported as negative for acid-fast bacilli. He was admitted to Bruns General Hospital on July 2, 1945 and eight days later had the onset of a severe pain in the right chest associated with cyanosis, tachycardia and dyspnea. X-ray films showed a complete collapse of the right lung field. Fluid and air were aspirated on numerous occasions from the right pleural space with improvement in symptoms. The sputum was consistently negative for acid-fast bacilli. *Coccidioides immitis* was cultured from

the chest fluid but the sputum was negative for *Coccidioides immitis* on many examinations. Blood serological examination for coccidioidomycosis was performed by Dr. Charles Smith of Stanford University in October and December 1945, and the report was negative for coccidioidal infection on each occasion. The lung remained almost completely collapsed and a right decortication was performed on January 23, 1947, almost nineteen months after the spontaneous pneumothorax. At the time of decortication, a bronchopleural fistula was discovered in the area of cavitation in the right upper lobe. The fistula and surrounding cystic area were removed by wedge resection. The pathological character of the cyst wall could not be determined. The lung completely reexpanded, except for a slight apical separation, and an apical thoracoplasty was performed on March 13, 1947. Blood serological examination was again performed at Stanford University in April 1947 and the complement fixation was positive in one to four titre. Patient was sent on a convalescent furlough in May 1947 at which time he was asymptomatic aside from chest pain. The area of consolidation in the right lower lobe remains unchanged.

The indications for surgery in this case were persistent cavitation with spontaneous pneumothorax, inexpandable lung and coccidioidal empyema.

Case 10: This 30 year old white male was born in Oklahoma and spent nine months in desert training in Arizona in 1939 and 1940 and three months on maneuvers in a desert area of California in 1941. On July 5, 1945 he was admitted to a general hospital in Newfoundland with productive cough, shortness of breath and fever. He was told that he had virus pneumonia. Symptoms cleared and he was discharged from the hospital on July 16, 1945. Two days later there was a small hemoptysis and he was hospitalized again. He continued to have a chronic cough productive of a small amount of mucoid sputum and in November and December 1945 there was blood streaked sputum on several occasions. On January 15, 1946 he coughed up about four ounces of blood. An x-ray film was taken of the chest and was said to be negative. On February 8, 1946 there was a severe pain in the left chest, with dyspnea and fever of 102 degrees. He was hospitalized and an x-ray examination of the chest showed a massive collapse of the left lung. Fluid and air were aspirated from the left chest but the lung failed to reexpand completely and he was transferred to Fitzsimons General Hospital on March 14, 1946. On admission the Mantoux test was negative on the first strength, doubtful on the second strength and numerous examinations for acid-fast bacilli were all reported negative. The coccidioidin skin test was positive in one to one hundred dilution and three positive cultures of *Coccidioides immitis* were obtained from the fluid aspirated from the left pleural space. The sputum was repeatedly negative on smear and culture for *Coccidioides immitis*. A left decortication was performed on July 7, 1946. A slight pneumothorax space existed following operation but his general condition was good and he was sent home on a thirty day furlough. On return, the lung was completely reexpanded. At the time of discharge from the hospital he was essentially asymptomatic.

The indications for surgery in this case were spontaneous pneumothorax with inexpandable lung and coccidioidal empyema.

SUMMARY

A total of ten cases are reported which have had surgery because of some complication of primary pulmonary coccidioidomycosis.

Six of these cases had lobectomy and four had decortication.

Of the six lobectomies performed, four were done because of persistent symptoms associated with pulmonary cavitation. These cases had symptoms for fourteen, thirty-five, thirty-six and sixty-two months, respectively and had been hospitalized because of these symptoms for an average of twelve months. The chief complaint of all four patients was a feeling of weakness and ease of fatigue. All had a dry chronic cough and three had hemoptysis frequently, however, the hemoptyses were not serious in any case. Three were underweight and failed to gain weight during their hospitalization. Two had chronic low grade fever and two had chest pain of a pleuritic nature. With the exception of the chest pain, all symptoms were relieved promptly by surgery.

One lobectomy was performed on a patient with a large cavity in one lung field and a small round lesion in the opposite lung. The cavity measured from six to eight cm. in diameter and contained a fluid level. There was no change in either lesion after ten months of hospitalization and, although the patient had no symptoms, the cavity was removed by lobectomy. The lesion in the opposite lung remains unchanged.

The remaining lobectomy was performed because of an undiagnosed solid tumor of the left upper lobe. Following lobectomy the diagnosis of coccidioidoma was established.

The four decortications were performed because of nonexpansile lung following spontaneous pneumothorax. The diagnosis of coccidioidomycosis had been established in three of these cases prior to the collapse of the lung, and all three had pulmonary cavitation. At the time of surgery, each of these cases was demonstrated to have a bronchopleural fistula at the site of the cavitation. In the remaining case the cause of the spontaneous pneumothorax was not proven, but *Coccidiodes immitis* was isolated from the pleural fluid following the spontaneous collapse of the lung.

The surgery was performed without undue difficulty and there were no serious complications during the operations or immediately postoperatively. There was no evidence of dissemination of the disease following surgery in any of the cases. There was incomplete expansion of the lung following decortication in two cases; an apical thoracoplasty was performed on one of these patients and the other preferred to have no further surgery. Both cases are doing well. One patient developed hemoptysis three months following a right upper lobectomy performed because of cavitation with associated symptoms which had persisted over a period of three years. He was re-hospitalized and x-ray films revealed an infiltration and a small cavity within the apical portion of the remaining right lung. His sputum was strongly

positive for acid-fast bacilli. Prior to surgery, tuberculin skin tests had been negative on first and second strengths and the sputum had been negative for acid-fast bacilli on twenty-one smears, ten cultures, and two guinea pig necropsies.

The mycelial form of *Coccidioides immitis* was identified within the cavities of four of the five cases having lobectomy for cavitation.

CONCLUSIONS

The primary form of coccidioidomycosis is such a benign condition that it has generally been considered to be a self-limited disease but there are rare cases for which surgery should be performed. We have used the following indications:

- 1) Spontaneous pneumothorax with a nonexpansile lung.
- 2) Solid tumor in the lung.
- 3) Persistent symptoms of weakness, ease of fatigue, chest pain, or hemoptysis in the presence of a persistent cavity.
- 4) Evidence of extensive pulmonary disease with or without symptoms.

RESUMEN

Se informa sobre diez casos en los que se intervino quirúrgicamente debido a alguna complicación de la coccidioidomicosis pulmonar primitiva. En seis de los casos se ejecutó una lobectomía y en cuatro un descortezamiento.

De las seis lobectomías, cuatro se llevaron a cabo debido a síntomas persistentes asociados con cavernas pulmonares. Estos casos tuvieron síntomas por catorce, treinta y cinco, treinta y seis, y sesenta y dos meses, respectivamente, y habían sido hospitalizados debido a estos síntomas por un promedio de doce meses. La queja principal de todos los cuatro pacientes fue una sensación de debilidad y fácil fatiga. Todos tenían una tos crónica seca y tres sufrían hemoptisis frecuentemente, aunque las hemoptisis no fueron graves en ningún caso. Tres estaban bajo de peso y no pudieron ganar en peso durante su hospitalización. Dos tenían fiebre baja y dos sufrían de dolor en el pecho de naturaleza pleurítica. Con la excepción del dolor en el pecho, la intervención quirúrgica alivió prontamente todos los síntomas.

Se llevó a cabo una lobectomía en un paciente con una caverna grande en un campo pulmonar y una pequeña lesión redonda en el pulmón opuesto. La caverna midió de seis a ocho cm. de diámetro y mostraba un nivel de líquido. No hubo cambio alguno en ninguna de las dos lesiones después de diez meses de hospitalización y, aunque el paciente no tenía síntomas, se extirpó la caverna mediante la lobectomía. La lesión en el pulmón opuesto continúa lo mismo.

Se llevó a cabo la otra lobectomía debido a que existía un tumor sólido no diagnosticado del lóbulo superior izquierdo. Subsiguiente a la lobectomía se estableció el diagnóstico de coccidioidoma.

Se ejecutaron los cuatro descortezamientos debido a pulmones faltos de expansión subsiguientes a neumotórax espontáneos. En tres de estos casos se había establecido el diagnóstico de coccidioidomicosis antes del colapso del pulmón y todos tres tenían cavernas pulmonares. Durante la operación se demostró que todos estos casos tenían fistulas bronco-pulmonares en el lugar de las cavernas. En el otro caso no se comprobó la causa del neumotórax espontáneo, pero se aisló el *Coccidioides immitis* del derrame pleural que siguió al colapso espontáneo del pulmón.

Se ejecutaron las operaciones sin mucha dificultad y no hubieron complicaciones graves durante la operación o en el periodo postoperatorio inmediato. No hubo signos de diseminación de la enfermedad subsiguiente a la operación en ninguno de los casos. En dos casos no se logró la expansión completa del pulmón después del descortezamiento; en uno de estos pacientes se ejecutó una toracoplastia apical y el otro prefirió que no lo operaran más. A ambos casos les va bien. Un paciente tuvo una hemoptisis tres meses después de una lobectomía superior derecha que se llevó a cabo debido a la existencia de una caverna acompañada de síntomas que habían persistido por un periodo de tres años. Se hospitalizó a este paciente de nuevo y las películas radiográficas revelaron una infiltración y una caverna en la parte apical del pulmón derecho restante. Se encontraron muchos bacilos ácido-resistentes en el esputo. Antes de la intervención quirúrgica las pruebas cutáneas a la tuberculina habían sido negativas con la primera y la segunda concentraciones y no se habían encontrado bacilos ácidosresistentes en el esputo en veintiún frotis, diez cultivos y dos autopsias de cobayos.

En cuatro de los cinco casos en los que se ejecutó lobectomías debido a cavernas se identificó la forma miceliana del *Coccidioides immitis* dentro de las cavernas.

CONCLUSIONES

La forma primaria de coccidioidomicosis es un estado tan benigno que generalmente se ha considerado ser una enfermedad que termina de por sí misma, pero hay raros casos en los que se debe intervenir quirúrgicamente. Hemos empleado las siguientes indicaciones:

- 1) Neumotórax espontáneo con pulmón falto de expansión.
- 2) Tumor sólido en el pulmón.
- 3) Síntomas persistentes de debilidad, fácil fatiga, dolor en el

pecho o hemoptisis cuando existe caverna persistente.

- 4) Signos de enfermedad pulmonar extensa con síntomas o sin ellos.

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Discussion

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This excellent paper which Captain Greer has presented this afternoon is very timely. Coccidioidomycosis, because of its comparatively infrequent occurrence, is not readily recognized. If tardy recognition of the disease be conceded in those certain areas where it is endemic in occurrence, a still more lagging recognition must be expected in those other parts of the United States where the disease rarely occurs. Although coccidioidomycosis previous to World War II had been considered peculiar to California, Arizona, New Mexico and Texas, it must now be thought of as having no certain geographic distribution. During the war many troops were stationed in the area covered by the above mentioned states and a certain percentage of these troops became infected with coccidioidomycosis. As a direct corroboration of this fact, Forbus, in his excellent monograph on this subject published in the *Military Journal* of November 1946, states that six thousand members of the armed forces developed this disease. Both the

known and the unknown cases are now scattered throughout the United States and they have originated a problem which the medical profession will be encountering for years to come. This paper by Captain Greer has served to alert us, and we will be aided in recognizing the cases which we do encounter because of the excellent description of the symptomatology and because of the careful notation of the physical evidences of the disease which the paper presents. However, I do not think we need fear coccidioidomycosis will become endemic throughout the country for the reason that the natural source of this infection seems to refer to certain wild animals that inhabit the Southwest; and of further importance, that the promotion of progress of the disease is related to the climatic conditions of that area. Neither the destruction of these animals nor a change in the climate is likely.

One of the most important points brought out by Captain Greer is his recognition of the present safety control through application of pulmonary resections in the treatment of the disease. Lobectomy, which at one time had a mortality of more than sixty per cent, can now be performed with an operative risk of less than one per cent. Pulmonary coccidioidomycosis can occur in the form of: 1) Caseous nodules in the lung. 2) Caseous granulomatous pneumonia with cavities. 3) Pulmonary cavity formations. 4) Granulomatous bronchial scarring.

I would like to add the caution that cases of coccidioidomycosis which are apparently arrested in their course may recur and may become disseminated in type, of which type more than fifty per cent terminates fatally. In summing up, it appears that Captain Greer's management of these cases is a definite step forward, and it also appears reasonable to assume that pulmonary resection may become the procedure of choice in the treatment of pulmonary coccidioidomycosis.

D i s c u s s i o n

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Incidence has an all important bearing on the possible surgical aspects of coccidioidomycosis. The prevalence of the fungus in the Southwest is well known. On the San Carlos Indian Reservation, Aronson found 98 per cent of adults react to coccidioidin. In the city schools of Phoenix our recent study showed 58 per cent of white high school students reacted and 66.1 per cent of junior college students. However the development of granulo-

matous lesions is rare. If 66 per cent of adults have been sensitized, approximately 200,000 people in the Phoenix area would be involved and yet 200 cases of clinically significant coccidioidomycosis found in Phoenix in five years would be an outside estimate.

There has come to my attention in Phoenix only four fatalities from this disease in the past six years. One is a case I will show you. The other three had primary infection passing rapidly into progressive miliary distribution of infection never revealing any localization of the lesions sufficient to consider a surgical approach. On all three the primary infection was a pneumonitis followed by lymphatic involvement of mediastinal and cervical nodes and coincidentally, progressively generalized disease—high temperature, toxemia, and central nervous system involvement with death in a few weeks to three months of onset.

We have made a diagnosis of coccidioidomycosis in 21 cases. Of these, five had cavity formation and in all but the one most recent case the cavity evolved into a round homogeneous shadow, with absence of symptoms. The lesions are innocuous in most cases and with no contagiousness of the disease there is no reason for removing them, unless they produce symptoms or complications. They seem relatively much less dangerous than tuberculomas from which they are difficult to distinguish.

Shipman of San Francisco wrote me of only one case of coccidioidomycotic granuloma treated surgically with removal by Brunn. Samson in Oakland, Calif. had no cases. John Jones of Los Angeles had one lobectomy years ago found to be coccidioidoides. Burford did a lobectomy for known coccidioidomycosis presenting multiple small annular lesions in one lobe, with a good result. Persistent sputum and positive cultures were the chief indications.

CASE REPORTS

Case 1: Richeson, a 24 year old woman who had a mild respiratory infection a few weeks before the first film was made. Sputum was scanty and several negative tuberculosis and coccidioides cultures were obtained. The tuberculin test was negative. The coccidioidin test was strongly positive, 1:1,000 dilution. The lesion has contained fluid and has not appeared entirely stable yet there have been no symptoms for three years. Lobectomy does not seem to be indicated.

Case 2: Hawthorne, a 63 year old man, presented a chief complaint of weight loss of 40 pounds in three months, lack of appetite and mild cough. Four sputum tests were negative for tuberculosis and coccidioides smears. Bronchoscopic inspection was negative. A diagnosis of carcinoma was made and exploratory thoracotomy performed. The solid irregular tumor mass in the lung appeared grossly as carcinoma. Pneumonectomy was performed. The specimen showed typical spherules of coccidioidomycosis granuloma. The patient died on the third postoperative day of respiratory insufficiency and pulmonary edema.

Lest anyone gain the impression that the surgical approach to coccidioidomycosis lesions will attain wide application I should like to say that few of us will see such situations as described by Drs. Greer and Grow. The importance of this paper is not diminished by the low incidence of the particular phases of the disease which have been described. New surgical techniques are here applied to coccidioidomycosis for the first time and are shown to be useful. The silent granulomatous lesions should not be treated surgically.

Cases of coccidioidomycosis requiring surgical therapy are limited to extensive persistent cavitory or granulomatous lesions with clinical symptoms of persistent cough and sputum, weight loss or pulmonary hemorrhage.

I should particularly like to point out the unprecedented and commendable way in which Dr. Grow successfully handled the distressing complications of coccidioidomycosis with cavity rupture.

Pulmonary Cryptococcosis

Report of a Case with Surgical Cure*

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Torulosis or cryptococcosis is a chronic disease affecting the lungs, central nervous system, skin, and lymph nodes. One of the earliest cases was described by Busse¹ in 1894 who designated the causative organism, *saccharomyces*. Many names have been applied to this disease which is also widely known as European blastomycosis. The present accepted nomenclature for the etiological agent is *cryptococcus neoformans* as suggested by the National Research Council.

In 1937, Levin² reported 60 cases referable to the central nervous system in which the prognosis was extremely poor. The disease ran a chronic course terminating fatally in about five or six months.

Up to the present time, well over a hundred cases have been reported³⁻⁵ and it appears from the literature that more are coming to light each year as our knowledge increases in the clinical and diagnostic phases of the disease.

As this is a case report, we feel that it is unnecessary to reiterate the characteristic clinical and pathological features of the disease. These phases are summarized adequately in the Manual of Clinical Mycology⁶ and elsewhere.

CASE RECORD

J.S., a white male, age 19, was admitted to Hahnemann Hospital May 6, 1943 with no particular complaint; however, he was referred from a sanatorium to the Department of Thoracic Surgery for a mass in the right lower lobe.

Past Personal History: He had the usual childhood diseases. He does not smoke or partake of alcoholic beverages excessively and drinks coffee and tea moderately. In 1941, he worked in a rolling mill where there was a great amount of coal dust, metal dust, and sulfur fumes. His last occupation was as a laborer in a CCC camp in Pennsylvania.

History of Present Illness: On January 2, 1943 he was called for Army induction examination and a mass-like lesion was found in the right lower lobe. He was rejected and asked to return in 2 to 6 months. He

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returned April 3, 1943 and was again rejected, but this time he was advised to go to a sanatorium. At the sanatorium he was studied for tuberculosis; however, all tests proved to be negative.

With the evidence for tuberculosis lacking, he was referred to the Thoracic Surgery Department at Hahnemann Hospital. Physical examination revealed a well nourished, white male. There was no evidence of jaundice, edema, cyanosis, or dyspnea. He was mentally alert and co-operative. Careful assay of all systems revealed no abnormalities. Examination of the chest disclosed no evidence of any lesion to palpation, percussion, and auscultation. The temperature, pulse, and respiratory rates were normal. Laboratory studies were fruitless except for the x-rays which confirmed the previous observations made at the Army induction center and the sanatorium.

The conclusion drawn by the Thoracic Surgery Department was lung tumor, probably bronchogenic carcinoma, and that surgical exploration was indicated. On May 12, 1943 the patient's chest was explored and a right pneumonectomy was performed. Recovery was uneventful and he was discharged on June 7, 1943 and advised to return at regular intervals for re-examination. He has been well with no complaints to the present time—a period of five years and seven months.

Pathological Examination

Gross: Specimen consists of the right lung measuring approximately 24 x 11.5 x 3.5 cm. The upper lobe is poorly aerated but appears grossly normal. The middle lobe is air containing and not remarkable. The lower lobe contains a large palpable, firm, rubbery mass measuring 4.5 cm. in diameter. It approximates very closely to the main median bronchus extending into the surrounding lung parenchyma. The mass on

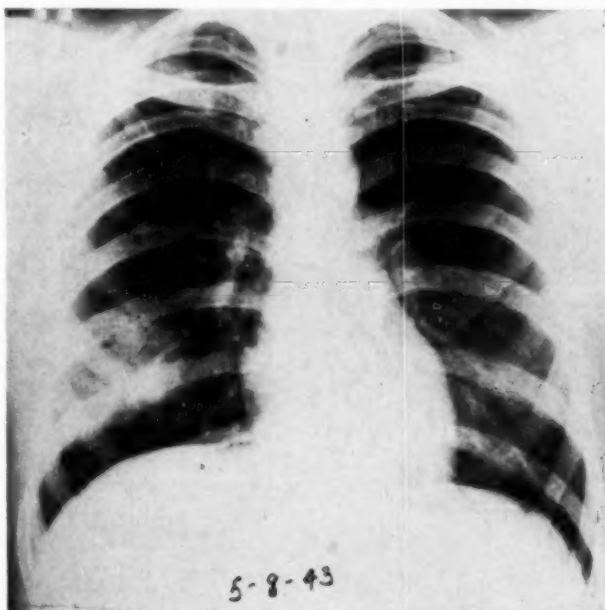


FIGURE 1
Mass-like lesion in the right lower lobe.

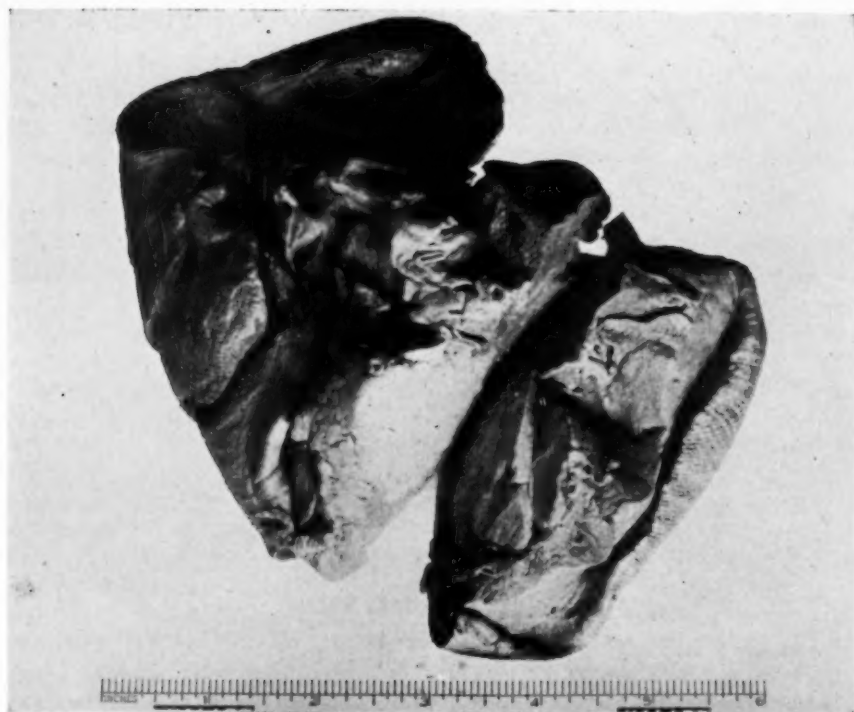


FIGURE 2: Right lung showing large grayish white, rubbery, well circumscribed lesion in the lower lobe.

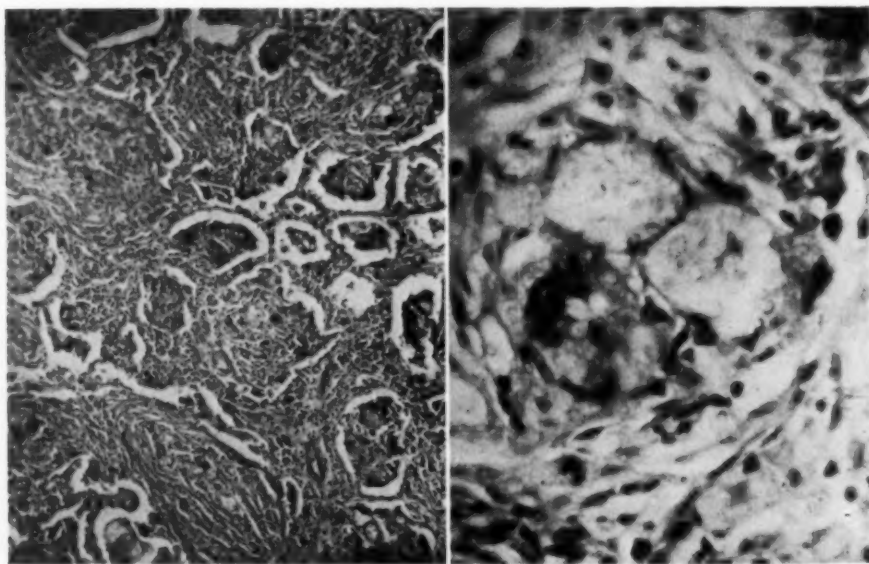


FIGURE 3

FIGURE 4

Figure 3: Photomicrograph showing typical granulomatous appearance. Also note tubercle pattern with giant cells. Phloxine methylene blue, X100.—*Figure 4:* Photomicrograph showing typical capsules containing refractile yeast bodies of *cryptococcus neoformans*. Phloxine methylene blue, X430.

section is grayish white, well circumscribed, firm, and rubbery. The tracheobronchial tree is not remarkable. One hilar lymph node is slightly larger than normal and on section has a grayish black hue.

Microscopic Examination disclosed a typical granuloma exhibiting areas of fibroblastic proliferation and lymphocytic infiltration resulting in a typical tubercle pattern, many of which contained foreign body giant cells. No evidence of caseation was noted. Many of the giant cells contained vacuoles. Scattered throughout the lesion there were noted large capsular spaces containing small, round refractile bodies, significant and suggestive of a fungus disease.

It was felt that this was either an atypical Boeck's sarcoid or a fungus disease. X-ray studies and the clinical findings did not support a diagnosis of Boeck's sarcoid and material was forwarded to Dr. Roger D. Baker of Duke University. His conclusions were: "The diagnosis of cryptococcosis is reasonably secure on the histopathologic study without culture in this case and I am listing it as No. 66 in our Fungus Disease registry." We have recently had a necropsy case of pulmonary and meningeal cryptococcosis and on comparative studies, the pulmonary lesions are very similar.

Comment

Analysis of many cases in the literature clearly indicates that cryptococcosis is a highly fatal disease.^{2,13} Statistical study of these cases disclosed that an extremely high percentage is of the meningitic type.^{2-5,13} The fungus gains entrance to the body through the respiratory tract.

Beck and Voyles⁸ found no beneficial effect from potassium iodide and sulfonamides in experimental torulosis of rats, guinea pigs, rabbits and dogs. Hobby, Meyer and Chaffee⁹ demonstrated in vitro sensitivity of the organism to penicillin; however, Harford¹⁰ reported a case treated with penicillin with no beneficial results. Mezey and Fowler¹⁴ claim beneficial results from 2 per cent alcohol intravenously; however, Voyles and Beck⁵ reported one case in which the course of the disease has been observed for seven years. Burger and Morton³ quoted several cases of apparently localized torulosis with cure. In these cases, the following sites were involved: muscles and spine,^{3a} inguinal abscess,^{3b} tongue,^{3c} nasopharynx,^{3d} and skin.^{3e} These cures were allegedly affected by curettement, iodides, and x-ray therapy. It is to be noted none of these presented any manifestation of pulmonary involvement.

Pulmonary cryptococcosis without meningeal involvement is unusual. Sheppe¹¹ reported a fatal case of pulmonary torulosis with necropsy findings. The brain and meninges, however, were not examined. Hardaway and Crawford¹² reported a case of pulmonary torulosis which they observed over a period of 15 months without meningeal involvement. Their roentgen studies, however, show progressive disease in both lungs over this period of time,

yet the patient was not too ill on discharge except for expectoration and cough. Dormer et al,¹⁵ in 1944 reported a case of cryptococcosis of the right lung in a 12 year old male child. The right lung and mass were removed. Postoperatively, however, meningeal symptoms developed and positive animal inoculation in the guinea pig was obtained from the spinal fluid. The meningeal symptoms responded to large doses of iodides and the patient was discharged two weeks later. It is suggested that if the disease is local and can be diagnosed and removed before meningeal spread has occurred, the patient may be cured. It is recommended that pulmonary lesions from which no tubercle bacilli can be isolated, be carefully studied for fungi.

SUMMARY

A case of pulmonary torulosis in a 19 year old white male is reported. The lesion presented as a granulomatous mass in the right lower lobe suspected of being tuberculosis or neoplasm. Pneumonectomy was performed with an uneventful postoperative course. The patient is perfectly well and at no time in the elapsed five years and seven months has there been evidence of meningeal spread. The left lung remains negative as of July 1948.

RESUMEN

Se informa sobre un caso de torulosis pulmonar en un joven blanco de 19 años. La lesión se presentó como una masa granulomatosa en el lóbulo derecho inferior, que se sospechó ser tuberculosis o neoplasma. Se llevó a cabo la neumonectomía con un curso postoperatorio sin novedad. El paciente está perfectamente bien y en los cinco años y siete meses que han pasado no ha mostrado ningún signo de extensión a las meninges. Hasta el mes de julio de 1948 el pulmón izquierdo sigue bien.

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A Method of Biopsy Useful in Diagnosing Certain Intrathoracic Diseases

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The difficulty in arriving at an accurate diagnosis in many patients with diseases of the lungs is well known. There are many adjuncts to a good history and physical examination, such as the x-ray, blood and sputum studies, bronchoscopy, thoracoscopy and examination of pleural exudates. At times these methods fail to give the diagnosis, and resort may be made to biopsy. This in the past has been done chiefly through the bronchoscope, thoracoscope, or by needle aspiration of intrapulmonary lesions. Removal of enlarged lymph nodes in the axilla, neck or other regions is a standard procedure and more recently cytological examination of the sputum has been helpful. When all these fail, and the answer is still not evident to the clinician, he may then consider the more heroic methods of obtaining tissue for study such as biopsy of the lung or of the hilar glands through an open thoracotomy incision. Before resorting to this latter procedure the following method of lymph node biopsy may be tried, and frequently a positive diagnosis will be made.

Under local anaesthesia an incision three centimeters long is made over the lateral border of the sternocleidomastoid muscle paralleling and just above the clavicle on the homolateral side of the pulmonary or chest disease (Fig. 1). In men the lateral aspect of the clavicular portion of the sternocleidomastoid may be divided. This may not be necessary when dealing with the less well developed muscle found in women. This muscle is then retracted medially and the fat filled space overlying the scalenus anticus muscle is entered.

This space is bounded below by the subclavian vein, medially by the internal jugular vein, and laterally by the omohyoid muscle. The floor of the space is formed by the scalenus anticus muscle with the phrenic nerve lying in its sheath. Several lymph nodes are found constantly in this fat pad and these are searched for and removed for microscopic study. One can then follow the subclavian and internal jugular vein down into the upper mediastinum and any node encountered can be removed. The only important structures which are encountered on the right side are the great veins and these must be treated with care. The phrenic

nerve lying deeply on the scalenus anticus is usually seen and should present no problem. The transverse cervical and the inferior thyroid vessels are usually encountered coursing through the fat, but these may be severed and ligated without complication to the patient. On the left side, in addition to the above structures, the thoracic duct may be encountered and care should be taken to avoid injuring this structure. The total procedure seldom takes more than a few minutes, and no special preoperative care or medication is necessary. The postoperative course is uneventful, and the minimum of discomfort is experienced by the patient.

The following five cases illustrate the use of this procedure. The first four of these patients presented signs or symptoms of pulmonary disease, but all of the usual examinations failed to lead to the correct diagnosis. The last case is presented because of its general interest.

Case 1: This 30 year old white male, noticed first in 1943 that his eyes were sore and watery. He ran a slightly febrile course and in March 1943, an x-ray inspection of his chest revealed bilateral hilar and right mediastinal adenopathy with slight pulmonary hyperemia or early infiltrate. Treatment was symptomatic plus small doses of x-ray irradiation to the mediastinum. By June 1943, he was much improved clinically, and returned to light work. In November 1943, x-ray inspection revealed the

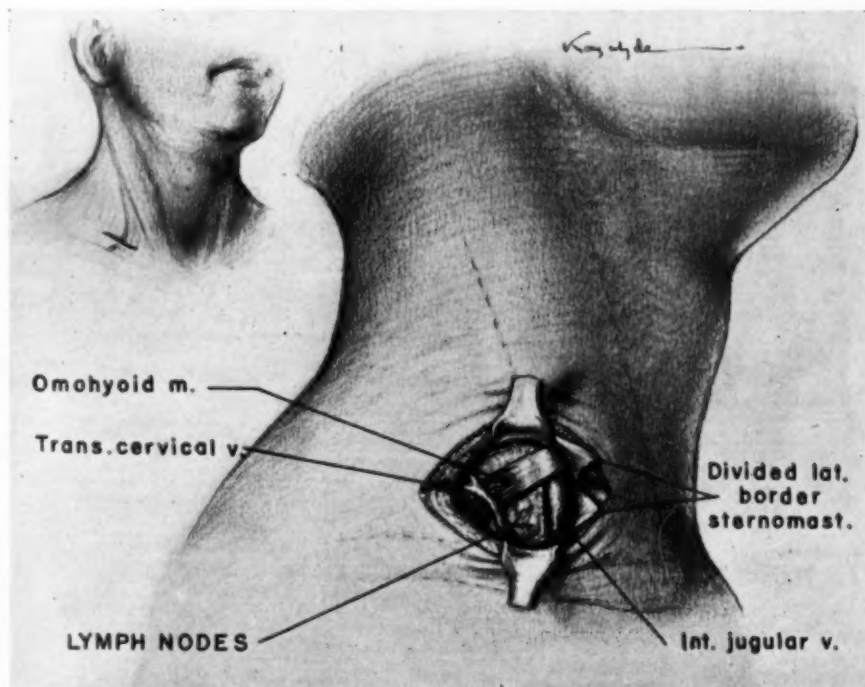


FIGURE 1: Insert shows the location and extent of the incision. Larger figure illustrates the anatomical major landmarks found at the level of the nodes.

mediastinal adenopathy to be improved but the pulmonary infiltrate was extending, bilaterally. He remained clinically well until he caught the "flu" in September 1945. An x-ray film of his chest at the time revealed extensive infiltration of both lungs, and a diagnosis of "far advanced tuberculosis" was made. When seen in December 1945, the patient complained of a slight cough on exertion, otherwise he felt well. Physical examination was entirely negative. Skin tests of tuberculin (1-100), histoplasmin, coccidioidin and echinococcus antigen were negative. Six gastric washings on concentration, culture and guinea pig inoculation were negative for the tubercle bacillus. The urine was negative. Blood counts and differential counts were all normal. Serum protein was 7.5 with an albumin globulin ratio of 4.5/3.0. X-ray films of the hands and feet were negative. X-ray films of the chest revealed extensive bilateral infiltration throughout both lungs (Fig. 2). Careful examination revealed no palpable lymph nodes in the neck or either axilla. Exploration of the right side of the neck, as outlined above, was done in January 1946, and four soft lymph nodes, the largest less than five millimeters in diameter, were removed from the neck. Pathological examination revealed lymph nodes containing multiple discrete noncaseating tubercles with multiple giant cells; no visible asteroid bodies (Fig. 3). Conclusion: Boeck's sarcoid.

Case 2: A 27 year old white female, had developed a slight persistent cough for over a month without sputum or fever. A chest x-ray inspection in January 1946, revealed an extensive infiltration of the right lung, with minimal involvement of the left (Fig. 4). She was then admitted to the hospital for further study. Her past history revealed lobar pneumonia in 1939. In 1940, a routine admission film to a nursing school was negative except for a "probable scar in the right lung; advise annual check." In 1941 an x-ray film of the chest was reported negative. She then carried

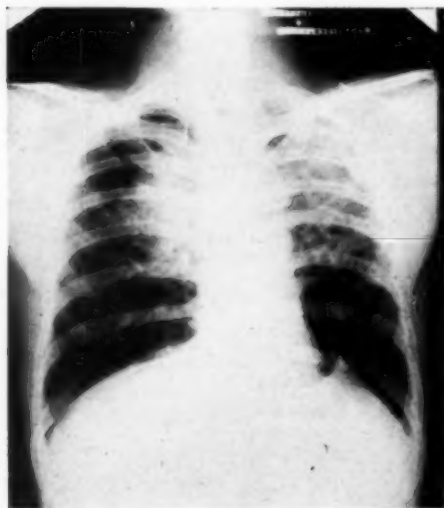


FIGURE 2

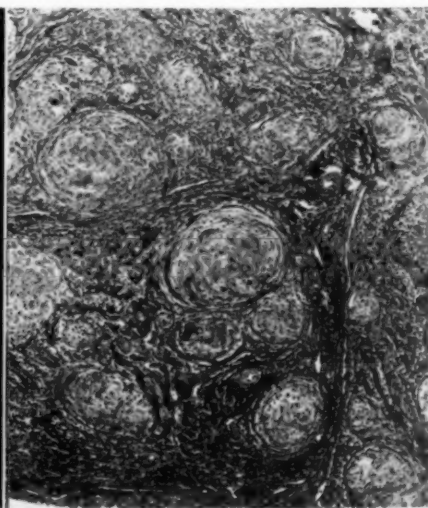


FIGURE 3

Fig. 2, Case 1: Note the bilateral hilar adenopathy and the infiltrate or lymphatic engorgement throughout both lung fields but more prominent on the left.—*Fig. 3, Case 1:* Note the replacement of the lymphoid tissue with tubercle-like structures and giant cells with no caseation, typical of Boeck's sarcoid.

through a normal pregnancy with birth of a normal child. A check x-ray inspection in 1944 was negative. Physical examination in January 1946, was entirely negative. Urine and routine blood studies were negative. Tuberculin test 1-100 was negative. X-ray films of the hands were negative. There were no palpable lymph nodes that were promising for biopsy, so the above exploratory operation was carried out and two small nodes measuring less than five millimeters in diameter were removed. Pathological examination revealed multiple discrete noncaseating tubercles typical of sarcoid (Fig. 5).

Case 3: E.T. This 65 year old white woman, had previously been well except for moderate hypertension. In July 1946, she first noticed a sense of pressure on her trachea and difficulty in breathing. A persistent hacking cough soon developed which was productive of small amounts of yellowish sputum. Physical examination revealed a well developed and nourished woman with the only abnormal findings being some dullness over the right apex with diminished breath sounds over this area. An x-ray film of the chest showed a density of irregular outline involving most of the apex of the right lung (Fig. 6). There were two small suspicious areas of infiltration in the upper lung field on the left. Bronchoscopy was negative. Sputum was negative for acid fast organisms, and for tumor cells. Intravenous pyelograms were negative. Gastrointestinal series and barium enema were negative. On August 1, 1946, biopsy was carried out using the method outlined above. A lymph node measuring eight millimeters in diameter was removed from beneath the sternum. Pathological examination revealed metastatic squamous cell carcinoma (Fig. 7). As a result of this positive finding, an exploratory thoracotomy for the tumor mass in the right upper lung field was not considered.

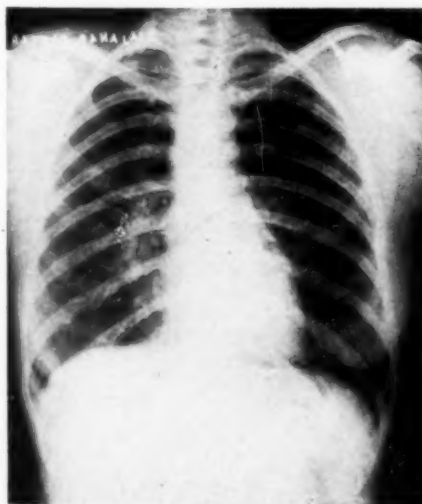


FIGURE 4

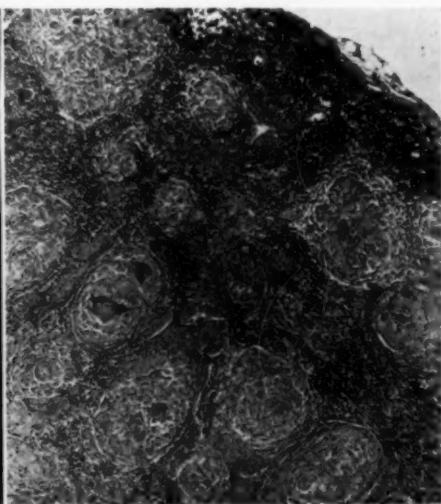


FIGURE 5

Fig. 4, Case 2: Note the diffuse and extensive infiltration of the right lung field with a minimal involvement of the left. The shadows are nonspecific.—
Fig. 5, Case 2: Note the similarity in the microscopic picture of this case with that shown in Figure 3.

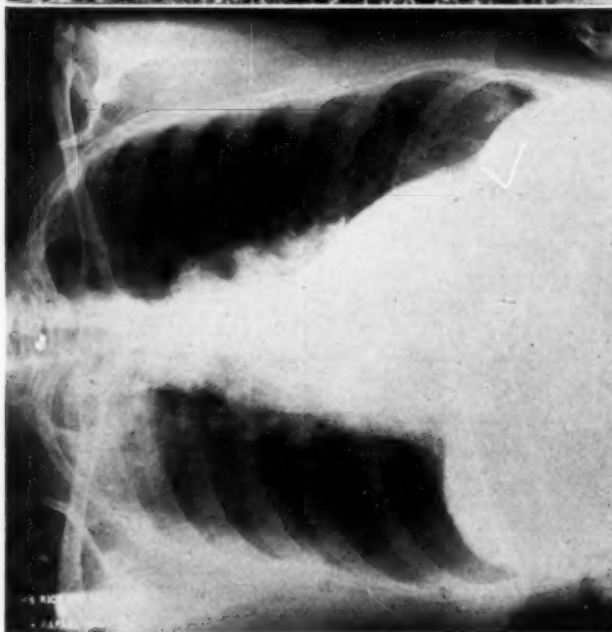
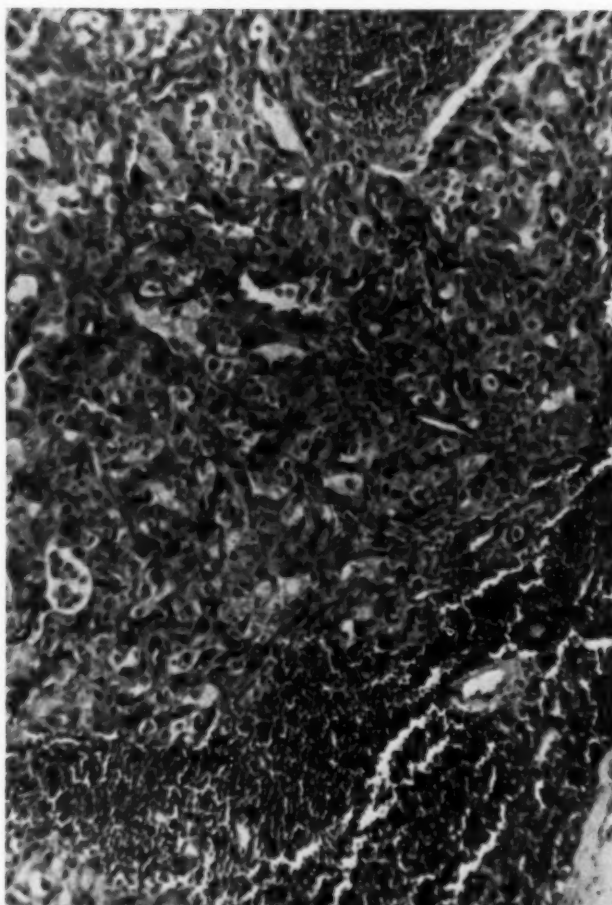
**FIGURE 6**

Fig. 6, Case 3: Note the lesion in the right upper lung field with probable mediastinal lymphadenopathy on the right. Small discrete densities on the left are suggestive of metastases.—Fig. 7, Case 3: Note the invasion of this node with carcinoma cells.

**FIGURE 7**

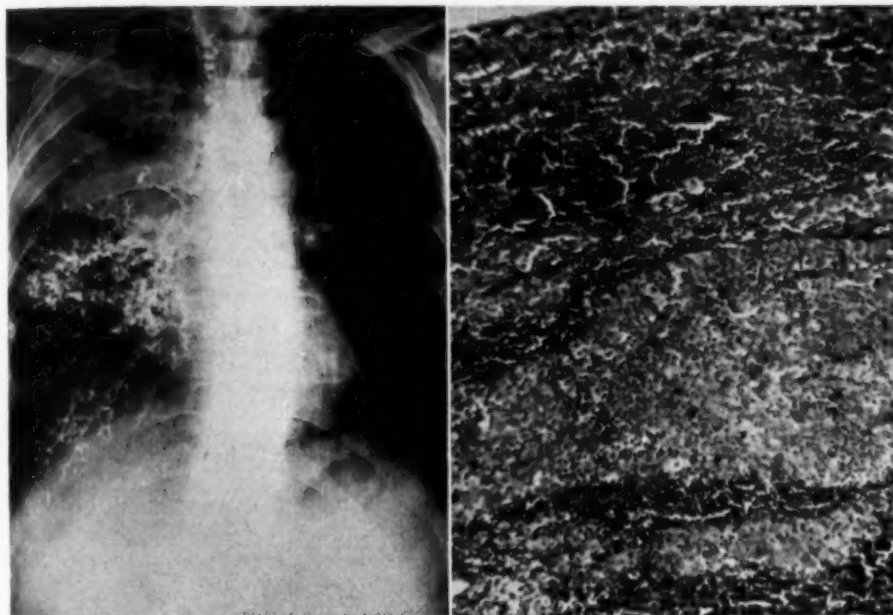


FIGURE 8

FIGURE 9

Fig. 8, Case 4: Bronchogram showing block of the right upper lobe bronchus with a poorly aerated upper lobe.—Fig. 9, Case 4: This again represents invasion of the lymph node by carcinoma cells and is similar to Figure 7.

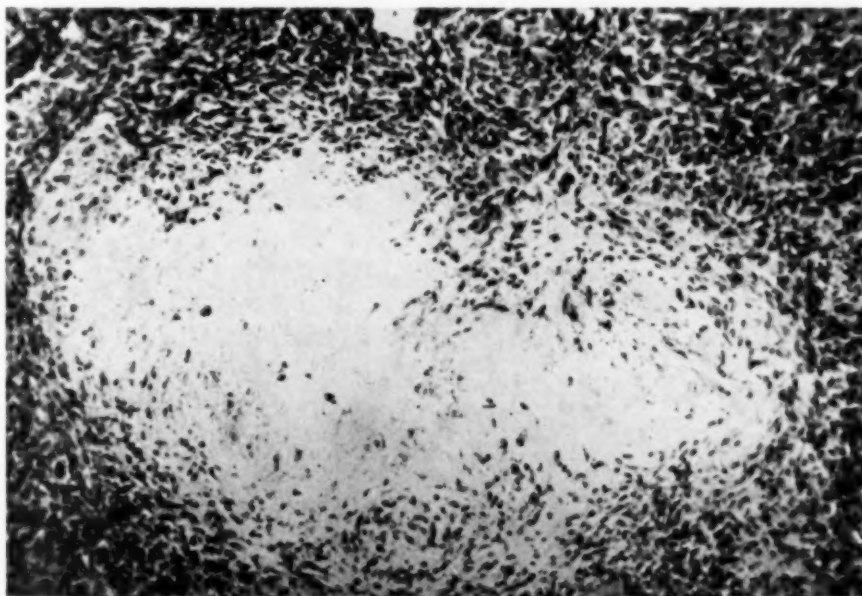


FIGURE 10: Note the tubercle-like formation with central necrosis and giant cells. With the use of Nicol prism refractive bodies are demonstrated which are consistent with silicosis.

Case 4: H.Z. This 68 year old man had been well until the first of October 1946, when he became ill with "pneumonia" of the right upper lobe. This failed to resolve, and six weeks later an x-ray inspection revealed a collapsed right upper lobe. Bronchoscopy was negative, but bronchograms revealed a block of the right upper lobe bronchus about 15 millimeters above its orifice (Fig. 8). Sputum examinations were negative for acid-fast organisms. Assuming that the patient had a carcinoma of the right upper lobe, an open thoracotomy was performed on November 27, 1946, hoping to remove the right lung. The lung was free, but many pleural implants were seen, and frozen section of one revealed squamous cell carcinoma. After the wound was closed, the biopsy procedure as outlined above was carried out, and three small nodes about four millimeters in diameter were removed. These all contained metastatic carcinoma (Fig. 9). If this latter procedure had been carried out first, the patient would have been saved an intratracheal anesthetic and the major surgical procedure of open thoracotomy.

Case 5: "L." This 59 year old patient has been a granite cutter for 30 years. He was seen for difficulty in swallowing incidental to a small hiatus hernia and a "peptic ulcer" of the lower esophagus. An x-ray film of the chest revealed diffuse silicotic changes, with several large densities interpreted as being conglomerate silicotic nodules. He had no complaints regarding his chest, but the biopsy procedure as outlined was carried out. Four small, hard lymph nodes measuring three millimeters in diameter were removed and on section typical silicotic changes were demonstrated (Fig. 10). Silica particles could be seen using Nicol prisms.

SUMMARY

Five cases are presented in which a lymph node biopsy was performed on nonpalpable, deeply situated nodes in the lower neck and upper mediastinum. A diagnosis of Boeck's sarcoid was established in the first two cases. The finding of metastatic carcinoma in the third case prevented a major surgical exploration of the chest. In the fourth case a major exploration was carried out only to find inoperable carcinoma of the lung with metastases. If biopsy had been carried out first this would not have happened. The fifth case illustrates the fact that silicosis as well as sarcoidosis and tumor advance as far as this group of nodes.

CONCLUSION

A method of biopsy of deep, nonpalpable lymph nodes of the lower neck and upper mediastinum is presented.

The operation is simple, requiring no special pre- or postoperative care and is done under local infiltration anesthesia.

These groups of nodes frequently contain the disease also present in the lung parenchyma, and in these cases a pathological diagnosis can be established.

RESUMEN

En cinco casos que se presentan se llevó a cabo una biopsia de ganglios no palpables situados profundamente en la base del cuello y en el mediastino superior. En dos casos de esos se hizo el diagnóstico de sarcoide de Boeck. El hallazgo de carcinoma metastásico evitó una operación mayor exploradora en el tórax. En el cuarto caso se llevó a cabo una operación exploradora mayor para solo encontrar un carcinoma inoperable del pulmón con metástasis. Si la biopsia se hubiese llevado a cabo antes, esto no habría ocurrido.

El quinto caso ejemplifica el hecho de que la silicosis tanto como la sarcoidosis y los tumores, llegan tan lejos que alcanzan estos grupos ganglionares.

CONCLUSION

Se presenta un método de biopsia de los ganglios profundos e impalpables de la base del cuello y del mediastino superior.

La operación es sencilla sin requerir cuidados pre o postoperatorios y es hecha bajo anestesia local por infiltración.

Estos grupos de ganglios a menudo contienen los cambios histológicos de la afección que radica en el pulmón y entonces un diagnóstico histopatológico puede hacerse.

The Pneumoconioses*

O. A. SANDER, M.D., F.C.C.P.
Milwaukee, Wisconsin

Definition: Dust added to lungs—no implication of fibrosis.

I. Organic Dusts:

A. Non-living:

1. Animal (dander, fur, hair, etc.)—allergic only, in occasional cases.
2. Vegetable (pollens, grains, cotton, etc.)—allergic only, if any reaction at all. (Byssinosis, bagassosis, tobaccosis—probably not toxic fibroses—lung changes more likely infectious pneumonitis or mechanical plugging of bronchioles by fibers).

B. Living:

1. Bacteria—Irritants, fibrogenic and allergic, occasionally occupational. Not true pneumoconioses.
2. Fungi—Same as above.

II. Inorganic Dusts:

Finely divided particulate matter. Particles must be less than 10 microns in diameter to reach alveoli; larger particles caught along upper respiratory tract. Phagocytosis of particles reaching alveoli.

A. Inert:

No fibrous reaction; dormant deposits in pulmonary lymphatics and root lymph nodes. Absorption of small dosages; deposition only after prolonged large doses. Visualized by x-ray when material is radiopaque.

1. Carbon (coal dust or smoke): Anthracosis.
2. Calcium (when excessive; small quantities absorbed): Calci-cosis.
3. Iron (when excessive, as after much confined welding, grinding, etc.): Siderosis.
4. Carborundum, emery, aluminum oxide, etc. (from artificial abrasive grinding wheels).
5. Aluminum (proposed use in prevention and treatment of sill-cosis).
6. Barium, tin, etc. (radiopaque deposits): Baritosis, etc.

B. Proliferative:

Fibrous tissue reaction in lymph nodes and nodules.

1. Free silica (SiO_2) as quartz, flint, etc. (typical fibrous nodules spread throughout both lungs): Silicosis.
 - a. Modified silicosis more common than classical, because most industrial dusts are mixtures of numerous components. Non-silica components tend to prevent development of typical fibrous nodules (Ca, Al, Fe, etc.).
 - b. No disability unless advanced or complicated with tuber-culosis.
 - c. Relationship of silicosis and tuberculosis primarily a reac-tivation and spread of pre-existing tuberculosis foci.
 - d. Relationship with heart disease—right heart strain only with advanced stages of silicosis and emphysema.
2. Asbestos (hydrated magnesium silicate): Asbestosis.
3. Other silicates? (talc, soapstone, mica, feldspar): Reported fi-brosis with some silicates probably due to quartz impurities.
4. Beryllium compounds.
 - a. Acute pneumonitis due to acid compounds.
 - b. Pulmonary granulomatosis due to fluorescent powers and possibly the oxides. Metallic beryllium inert.

*Presented at a Round Table Luncheon at the 15th Annual Meeting, American College of Chest Physicians, Atlantic City, N. J., June 5, 1949.

EDITORIAL

* FIRST NATIONAL CANCER CONGRESS

On February 25, 26 and 27, 1949 the first National Cancer Conference was held at the Hotel Peabody in Memphis, Tennessee. This Conference was sponsored by the American Cancer Society and the National Cancer Institute of the U. S. Public Health Service. Several hundred delegates representing fields of clinical cancer, investigation, and education-control were invited to pursue the objectives of this Conference. These objectives were: 1) To determine the present status of the early diagnoses and curability of cancer by site; 2) To summarize the present activities of investigators in fundamental and clinical cancer research involving etiology and epidemiology, diagnosis, new methods of treatment, etc.; 3) To appraise avenues of future efforts in clinical and investigative fields; 4) To determine what can be done to improve the control of cancer using methods now at hand.

Emphasis was placed on informal panel discussions. Of particular interest to the American College of Chest Physicians were the two panels on lung cancer. Alton Ochsner, M.D., F.C.C.P., was moderator of the first discussion. The agenda of this discussion included the incidence of lung cancer, diagnostic procedures, treatment, reporting of lung cancer, and problems in control. During this meeting Richard A. Overholt, M.D., F.C.C.P., suggested that the American College of Chest Physicians and the Trudeau Society cooperate with the sponsors of the Conference in a case finding survey. A second panel on lung cancer was devoted to laboratory studies. The following subjects were reviewed: 1) Inbred strain of mice and their pulmonary tumor incidences; 2) Pathology and histogenesis of experimental pulmonary tumors in mice; 3) Extrinsic factors influencing the development of lung tumors; 4) Intrinsic factors; 5) Pulmonary tumors in species other than human beings and mice.

The sponsors of this Conference are to be congratulated for providing the opportunity for appraisal of work on a national scale in oncology. New ideas were presented and for many who attended new avenues were opened for progress and development.

Seymour M. Farber, M.D., F.C.C.P.

Annual Meeting, Board of Governors

The Board of Governors of the College held its annual meeting at the Ambassador Hotel, Atlantic City, on June 2nd. The meeting was called to order at 10:00 a. m. by Dr. Carl C. Aven, Atlanta, Georgia, Chairman. The meeting was attended by the following Governors, alternates and invited guests:

Alabama: William S. Armour, M.D., Birmingham.
Arkansas: Harvey Shipp, M.D., Little Rock.
California: Buford H. Wardrip, M.D., San Jose.
Colorado: Arnold Minnig, M.D., Denver.
Delaware: Gerald Beatty, M.D., Wilmington.
District of Columbia: Edgar W. Davis, M.D., Washington.
Florida: M. Jay Flipse, M.D., Miami.
Georgia: Carl C. Aven, M.D., Atlanta (Chairman).
Illinois: Italo F. Volini, M.D., Chicago.
Indiana: Jerome V. Pace, M.D., New Albany (alternate).
Kentucky: T. Ashby Woodson, M.D., Louisville.
Maine: Francis J. Welch, M.D., Portland.
Maryland: Otto C. Brantigan, M.D., Baltimore.
Massachusetts: Hubert A. Boyle, M.D., New Bedford.
Michigan: Willard B. Howes, M.D., Detroit.
Minnesota: Karl H. Pfuete, M.D., Cannon Falls.
Mississippi: Robert E. Schwartz, M.D., Hattiesburg.
Missouri: Alfred Goldman, M.D., St. Louis.
Nebraska: Max Fleishman, M.D., Omaha.
New Jersey: Irving Willner, M.D., Newark.
New York: George Foster Herben, M.D., Yonkers.
North Carolina: Merle D. Bonner, M.D., Jamestown.
Ohio: David W. Heusinkveld, M.D., Cincinnati.
Oklahoma: Robert M. Shepard, M.D., Tulsa.
Oregon: James M. Odell, M.D., The Dalles.
Rhode Island: Frank A. Merlino, M.D., Providence (alternate).
South Dakota: William L. Meyer, M.D., Sanator.
Tennessee: David H. Waterman, M.D., Knoxville.
Texas: Alvis E. Greer, M.D., Houston.
West Virginia: Charles E. Smith, M.D., Terra Alta (alternate).

U. S. Army: Arden Freer, M.D., Washington, D. C.
U. S. Navy: Robert O. Canada, Comdr., Washington, D. C.
U. S. Public Health Service: Robert J. Anderson, M.D., Washington, D. C.

Hawaii: William F. Leslie, M.D., Hilo.
Puerto Rico: Jaime F. Pou, M.D., Hato Rey.

Canada

(Eastern Provinces): John J. Quinlan, M.D., Kentville, N. S. (alternate).
(Ontario): H. I. Kinsey, M.D., Toronto.

Portugal: Lopo de Carvalho, M.D., Lisbon.

Invited Guests:

Donato G. Alarcon, M.D., Mexico City, Mexico.
Richard H. Overholt, M.D., Brookline, Massachusetts.
Joseph C. Placak, M.D., Cleveland, Ohio.
Burt Shurly, M.D., Detroit, Michigan.
Paul A. Turner, M.D., Louisville, Kentucky.

After the signing of the College Register, Dr. Aven introduced Dr. Overholt, President of the College, who spoke for a few minutes on the activities of the College during the past year. Dr. Alarcon, Regent of the College for Mexico, was then introduced and invited to address the Governors. Dr. Alarcon expressed the regrets of Dr. I. Cosio Villegas,

Governor of the College for Mexico, for not having been able to attend the meeting. He presented a brief talk about the progress of the College in his country.

The next speaker to be introduced was Dr. Turner, Chairman of the Board of Regents of the College. Dr. Turner discussed the revisions made in the College By-Laws, especially as they pertain to the broad aspects of diseases of the chest. Under the revised by-laws, physicians having experience in the diagnosis and treatment of chest diseases are eligible for Associate Membership in the College. Dr. Turner pointed out that under these conditions membership in the College is open to cardiologists and other physicians practicing in fields relating to diseases of the chest. He suggested that the revised qualifications of Associate Members be kept in mind by the Governors when inviting physicians to membership in the College. Qualifications for Associate Membership in the College as they appear in the revised By-Laws are as follows:

- (a) He shall be more than 25 years of age;
- (b) He shall have received his degree of Doctor of Medicine at least two years prior to his election to the College;
- (c) He shall be prepared to furnish a written statement setting forth his qualifications and fitness for becoming an Associate Member of the College;
- (d) He shall have had at least two years' experience in the diagnosis and treatment of diseases of the chest.

Dr. David W. Heusinkveld, Cincinnati, Governor of the College for Ohio, was elected by the Board of Governors as their representative on the Committee on Nominations.

Dr. Carl C. Aven was re-elected as Chairman of the Board of Governors for the ensuing year.

Report of the Committee on Membership

As of June 1, 1949, there were 2903 members in the College, and 63 applications for membership were pending investigation. This is an increase of 325 new members admitted into the College during the past year. Of the 2903 members, 2060 are Fellows of the College, 175 are Associate Fellows, and 668 are Associate Members. Our increase represents 200 Fellows, 36 Associate Fellows and 89 Associate Members.

In the United States of America and its possessions, there are 2034 members, while in countries outside of the United States, there are 869 members. Our membership in other countries is distributed in 55 countries. Since the report of the Membership Committee in 1948, new members have been admitted from eight additional countries.

Chevalier L. Jackson, M.D.,
Chairman, Committee on Membership.

College Chapter News

INDIANA CHAPTER

The Indiana Chapter of the College will meet at the time of the annual convention of the Indiana State Medical Association to be held at the Murat Temple, Indianapolis, Indiana. A luncheon is planned for Thursday, September 22nd.

The principal speakers will be Merle Bundy, M.D., Director of the Division of Tuberculosis Control of the State Board of Health, whose subject will be "What Procedures Shall be Used for the Tuberculosis Follow-up of Children Under Fifteen Years of Age," and Hubert B. Pirkle, M.D., F.C.C.P., of the Indiana State Sanatorium, Rockville, Indiana, who will talk on "Results of Para Aminosalicylic Acid Treatment in a Series of Cases."

Following general discussion, an x-ray conference is scheduled; all members are urged to bring interesting films.

KENTUCKY CHAPTER TO BE ORGANIZED

Plans are being made for a meeting of the members of the College in Kentucky which will be the organizational meeting of the Kentucky Chapter. The meeting is to be held in Owensboro on Thursday, October 6, at the time of the annual meeting of the Kentucky State Medical Association. Hugh. L. Houston, M.D., F.C.C.P., Murray, Kentucky, President-Elect of the Kentucky State Medical Association, is arranging a breakfast meeting for the members. Richard H. Overholt, M.D., F.C.C.P., Brookline, Massachusetts, Past-President of the College and Chairman of the Council on Pan American Affairs, will present a paper at the meeting of the Kentucky State Medical Association and will also be present at the meeting of the new chapter.

MICHIGAN CHAPTER

The Michigan Chapter of the College will meet in conjunction with the Michigan State Medical Society in Grand Rapids, Michigan on September 22. The meeting, in the form of a dinner, social and business meeting, will be held at the Pantlind Hotel. The principal speaker will be George W. Wright, M.D., F.C.C.P., Saranac Lake, New York, who will speak on pneumoconiosis.

PENNSYLVANIA CHAPTER

The Pennsylvania Chapter of the College will meet on Saturday, October 22, at Devitt's Camp, Allenwood, Pennsylvania, upon invitation of Dr. John S. Packard, Medical Director. The meeting will consist of a noon luncheon followed by the scientific program. The program will comprise three papers by members of the staff of the institution and three papers by other members of the chapter.

ROCKY MOUNTAIN CHAPTER

The Rocky Mountain Chapter of the College will hold its annual meeting at the Shirley Savoy Hotel, Denver, Colorado, on Tuesday, September 20. The Colorado State Medical Society will meet in annual session at Denver, September 20-23. The following program will be presented at the chapter meeting:

Morning Session

"Intermittent Dosage Schedule of Streptomycin for the Treatment of Pulmonary Tuberculosis,"

Colonel Carl W. Tempel, Chief of the Tuberculosis Division, Medical Service, Fitzsimons General Hospital, and Vern Dyke, M.D., Ward Officer, Tuberculosis, Fitzsimons General Hospital.

"Problems in the Management of Ineffective Pneumothorax,"

B. T. McMahon, M.D., F.C.C.P., Denver, Colorado.

"Pulmonary Function Studies Following Decortication,"

Robert Brown, M.D., Chief of Thoracic Surgery Section, Fort Logan Veterans Hospital.

"Non-Tuberculous Infections of the Lung,"

Alvis E. Greer, M.D., F.C.C.P., Clinical Professor of Medicine, Baylor University College of Medicine, Houston, Texas.

Luncheon — Symposium

"Fungus Diseases of the Chest,"

Edwin R. Levine, M.D., F.C.C.P., Chicago, Illinois.

Alvis E. Greer, M.D., F.C.C.P., Houston, Texas

Colonel Hugh W. Mahon, Chief of the Pathology Department, Fitzsimons General Hospital.

Charles F. Taylor, M.D., F.C.C.P., Medical Director, Kansas State Sanatorium, Norton, Kansas.

Afternoon Session

"Treatment of Pulmonary Tuberculosis with Antihistaminic Drugs,"

Allan Hurst, M.D., F.C.C.P., Medical Director, National Jewish Hospital, and Tovy Millner, M.D., Fellow, National Jewish Hospital.

"Association of Bronchial Infection with Pulmonary Emphysema,"

Edwin R. Levine, M.D., F.C.C.P., Attending Physician, Michael Reese Hospital, Chicago, Illinois.

There will be no registration fee and all physicians are cordially invited to attend the meeting.

SECOND ARGENTINE CONGRESS OF TUBERCULOSIS

The following communique was received from Gumersindo Sayago, M.D., F.C.C.P., Regent of the American College of Chest Physicians in the Argentine, and President of the Second Argentine Congress of Tuberculosis.

It gives me a great deal of pleasure to bring before your attention that the Second Argentine Congress of Tuberculosis, over which I have the honor to preside, will be held in Cordoba on November 28-30, 1949. The following will be the official themes of the Congress:

1. Technique and Results of BCG Vaccination.
2. Antibiotics in the Treatment of Tuberculosis.
3. Tuberculosis of the Serous Membranes.

At the same time I would like to inform you of the official speakers for the above-mentioned topics:

1. Technique and Results of BCG Vaccination.

Speakers: Carlos A. Urquijo, M.D., Justo Lopez Bonilla, M.D., Abraham Schottlender, M.D., Isaias Naput, M.D., Miguel Setaro, M.D., Rogelio Clement, M.D., Paulino A. Rojas, M.D., Gumersindo Sayago, M.D., F.C.C.P., A. P. H. Degoy, M.D., Alberto Chattas, M.D., F.C.C.P.

2. Antibiotics in the Treatment of Tuberculosis.

Speakers: Francisco Arambarri, M.D., Jose Belingi, M.D., Mario A. Chaneton, M.D., Juan M. Laplace, M.D., Arturo Molina, M.D., Tomas de Villafañe Lastra, M.D., F.C.C.P., Raul Ortiz, M.D., Angel Bai, M.D.

3. Tuberculosis of the Serous Membranes.

Speakers: Juan M. Gonzalez, M.D., Angel Invaldi, M.D., B. Manuel Pardo, M.D., Jose Peroncini, M.D., Rodolfo Cucchiani Acevedo, M.D., Alfredo Lanari, M.D., Carlos G. Puga, M.D., Enrique Ferrari, M.D., Juan B. Rocca, M.D., Isaac F. Wolaj, M.D., Julio Escarguel Malbran, M.D.

The registration fee for physicians is \$20.00. Interested physicians seeking further information, kindly write to the Secretary, Santa Rosa 974, Cordoba, Argentina.

Those physicians who plan to attend and desire to present a scientific paper, should notify the Secretary one month in advance, giving the title and an abstract of paper. The papers should be on one of the three official topics and should not exceed 15 minutes.

PERUVIAN SOCIETY OF TUBERCULOSIS

Ramon Vargas Machuca, M.D., F.C.C.P., has notified the College of the newly elected officers of the Peruvian Society of Tuberculosis for 1949 - 1950:

President: Luis Cano Girona, M.D., F.C.C.P.

Vice-President: Max Espinoza Galarza, M.D.; F.C.C.P.

Secretaries: Ramon Vargas Machuca, M.D., F.C.C.P.

Victor Narvaez Obeso, M.D.

Treasurer: Segundo Huaco Vizcardo.

Librarian: Juan Jose Arredondo, M.D.

ECUADORIAN SOCIETY OF TUBERCULOSIS

The newly elected officers of the Ecuadorian Society of Tuberculosis for 1949 - 1950 are:

President: Marco Martinez Macias, M.D.

Vice-President: Ernesto Briones, M.D.

Secretary, Alfonso Blum Martinez, M.D.

Secretary (Scientific Sessions): Jose Durand Nicola, M.D.

Treasurer: Juan J. Villacis P., M.D.

Librarian: Efren Jurado Lopez, M.D.

Counsellors: Jaffre Lara M., M.D.

Counsellors: Jaffre Lara M., M.D. and Emilio Jaramillo, M.D.

College News Notes

Dr. William S. Klein, formerly Assistant Director of the Chest Service, Michael Reese Hospital, Chicago, Illinois, has accepted appointment as Medical Director of the J.C.R.S. Sanatorium, Spivak, Colorado. Dr. Klein took over his duties at the sanatorium on September 1st.

Dr. George H. Jurgens, Milwaukee, Wisconsin, addressed the Clark County Medical Society on "Bronchograms Can be Done in the Office" on June 10th.

Dr. J. Karl Poppe, Portland, Oregon, Assistant Clinical Professor of Surgery, University of Oregon Medical School, will participate in the Fourth Annual Postgraduate Cancer Course being presented in Portland, September 12-16, by the Oregon Division, American Cancer Society and the University of Oregon Medical School. Dr. Poppe's subject will be "Lung and Intrathoracic Cancer; Diagnosis and Treatment."

The following members of the College exhibited oil paintings, water color paintings and photography at the Eleventh Annual Exhibition of the American Physicians Art Association in Atlantic City last month: Dr. Henry Bachman, Malta, Ohio; Dr. Ethan Allan Brown, Boston, Massachusetts; Dr. Robert W. Clarke, San Rafael, California; Dr. Clyde W. George, Buffalo, New York; Dr. Bernard Klein, Joliet, Illinois; Dr. T. E. Newell, Dayton, Ohio; Dr. Jacob Jesse Singer, Beverly Hills, California; and Dr. A. J. Steiner, St. Louis, Missouri.

Dr. Victor Yespica of Caracas, Venezuela has received a fellowship for postgraduate study at the Los Angeles Sanatorium, Duarte, California. Dr. Yespica spent the past year in Chicago taking postgraduate study at Michael Reese Hospital, the Municipal Tuberculosis Sanitarium, Winfield Sanitarium and the Veterans Hospital at Hines, Illinois.

CONTINUATION COURSE IN DISEASES OF THE CHEST

The University of Minnesota announces a continuation course in Diseases of the Chest to be presented on October 20, 21 and 22, 1949. The course is sponsored by the Minnesota Chapter of the American College of Chest Physicians and is intended for general physicians. The course will be held at the Center for Continuation Study on the Minneapolis campus of the University.

Among the subjects to be presented will be "The Work-up of a Patient with an Abnormal Chest X-ray Shadow," "The Differential Diagnosis of Cardiac and Pulmonary Dyspnea," "The Psychosomatic Aspects of Chest Diseases," and "Acute Respiratory Diseases." Symposia will be held on pulmonary tuberculosis and carcinoma of the lung. A clinical x-ray conference and medical clinic will be held on chest diseases.

Dr. O. A. Sander, Milwaukee, Wisconsin, will discuss "The Pneumoconioses," as a visiting faculty member for the course. Clinical and full-time members of the staff of the University Medical School and the Mayo Foundation will complete the faculty for the course.

Book Reviews

ESSENTIALS OF PUBLIC HEALTH. By William P. Shepard, B.S., M.D., M.A. With the collaboration of Charles Edward Smith, M.D., D.P.H., Rodney Rau Beard, M.D., M.P.H. and Leon Benedict Reynolds, A.B., Sc.D. With a foreword by Ray Lyman Wilbur, M.D., L.L.D., Sc.D. 600 pages. Cloth. J. B. Lippincott Company, Philadelphia, 1948.

This book of 600 pages is intended for the physician engaged in private practice, the medical student and members of allied professions. It contains much fine material of value to physicians in diseases of the chest. For example, among the food-borne diseases are amoebic dysentery, brucellosis, tularemia, tuberculosis, scarlet fever, trichinosis, influenza and colds; also diseases transmitted by insects and rodents like the rickettsial diseases, particularly Rocky Mountain spotted fever, tularemia, bubonic plague and trichinosis, all of which may cause chest lesions.

In the section on occupational health, attention is called to the fact that the average number of days absent from illness per person per year is about eight for males and 12 for females. Respiratory diseases ordinarily account for about 65 per cent of all absences due to illness among men, colds and cough making up nearly half of them, influenza nearly a fourth, laryngitis, tonsillitis and bronchitis about a fifth. Silicosis and asbestosis are discussed, with particular reference to prevention.

About 45 pages are devoted to tuberculosis with emphasis on preventive measures that have been so successfully employed in the past. It is pointed out that if the mortality rates of 1900 had continued to the present, nearly one-third of a million more persons in the United States would die each year from this disease than at present.

This is an excellent book by one of America's foremost authorities on public health. Physicians in diseases of the chest everywhere will find it of true value in solving many problems.

SURGICAL EXTRAPLEURAL PNEUMOTHORAX by Donato G. Alarcon, Imprenta Universitaria, Mexico, 1948.

No one in the Western Hemisphere has had a greater or a more successful experience with the use of extrapleural pneumothorax than the author. Dr. Alarcon has not only given us the benefit of his own vast experience, but he has assembled data from the German, French, and Spanish literature and has made it available in an English volume.

The most valuable service that a reviewer of this book can give is to strongly urge all doctors who make decisions about the program of treatment for the tuberculous sick to become familiar with the concepts set forth in this book. There is ample evidence presented to show that we have in the creation of an extrapleural space with air, then later oil filling, an effective method of controlling certain pulmonary lesions. The subject has been so controversial that it is impossible to set forth all the arguments—pro and con—but, if one reads the book or if one visits the Sanatorio San Angel, in Mexico City, it will be perfectly clear why Dr. Alarcon has been able to succeed in restoring health to so many patients with complicated and extensive bilateral forms of tuberculosis by this

method. After watching him operate and after observing results at first-hand, it is apparent to me that the following points are important reasons for his success.

- (1) The creation of a large initial space, with final adjustment of the size of the space to the requirements of the individual case.
- (2) Temporary drainage of the space by a catheter in order to easily control pressures and remove liquid.
- (3) Early conversion to a permanent form of collapse to eliminate the risk of late space infections.
- (4) Insertion of the space-occupying material after adjustment of the degree of collapse has been accomplished with air and after the extrapleural cavity walls have thickened.
- (5) The use of liquid (oil) material for space occupancy, for it conforms perfectly to the contour of the space.
- (6) Personal and meticulous attention to all details in the post-operative period.

The appearance of "Surgical Extrapleural Pneumothorax" has re-kindled my interest in a valuable method of collapsing the tuberculosis lung that stands somewhere between Forlanini's intrapleural pneumothorax and the permanent type of collapse that thoracoplasty provides. Every chest specialist would benefit greatly by an acquaintance with Dr. Alarcon's work.

Richard H. Overholt, M.D.

WHY DO PATIENTS IN TUBERCULOSIS HOSPITALS LEAVE AGAINST MEDICAL ADVICE by Godias J. Drolet and Donald E. Porter, published by New York Tuberculosis Association, 386 Fourth Avenue, New York 16, New York. This timely study is made up of sixty-six varityped pages, paper bound. It contains several statistical tables, an introduction, two main sections and a short chapter of recommendations,

For some time those interested in the tuberculosis problem in the general metropolitan area of New York, as indeed elsewhere in the country, have had a growing awareness of the serious aspects of tuberculous patients leaving institutions against medical advice. This publication is a statistical review of a study made by the Joint Committee on Patients Leaving Against Advice representing the Tuberculosis Sanatorium Conference of Metropolitan New York, the Department of Health, Hospitals and Welfare of the City of New York and other agencies. The study covers a.m.a. discharges for the calendar year 1947 from four representative institutions in that area with a combined bed capacity of 1,331. From these four institutions there were, that year, 1,828 discharges of which 674 or 37 per cent left against medical advice.

In the first main section of the report the matter of all discharges from these institutions during 1947 is analyzed statistically with particular emphasis on the group leaving against advice. The problem is considered as to race, sex, age, marital status, frequency of previous hospitalizations for tuberculosis, length of stay in the hospital before leaving against advice, physical condition on admission and on discharge, sputum content, etc.

The second section presents a detailed analysis of reasons given on the patient's record for leaving the hospital against medical advice. These are compared with additional reasons found by case-workers interviewing the patient and his family in the home or elsewhere, after

he or she left the hospital. These causes were coordinated and tabulated. There is also much discussion of the various conditions existing in the four institutions with considerable emphasis placed on the size of the professional staff, facilities for social service appraisals, occupational therapy and rehabilitation.

This section is followed by recommended changes which it is hoped will lessen the percentage of a.m.a. discharges in the Metropolitan New York Area. While these recommendations for the most part are pertinent, some of them, particularly those having to do with an adequate number of professional personnel will be difficult to meet in many parts of the country at the present time. On the whole, however, the study is thorough, logical and well executed. It is advisable that all sanatorium physicians, nurses, and those interested in the personal problems of patients confined to tuberculosis institutions be familiar with it. Yet, one might wish that its scope had covered a wider range of institutions throughout the nation. This has become an ever present problem although often not as serious at some institutions as it appears to be in the Metropolitan District in New York. Future studies of similar nature might bring to light factors in the milieu of this heavily populated area that has tended to intensify the problem.

Russell S. Anderson, M.D., F.C.C.P.,
Chairman, Council of Tuberculosis Hospitals,
American College of Chest Physicians.

Obituaries

VICTOR FRANCIS CULLEN

1881 - 1949

Dr. Victor Francis Cullen was born on September 5, 1881 at Hagerstown, Maryland, the son of Martin Emmit and Margaret Eva Cullen. Undergraduate and graduate study was taken at Rock Hill College where he received Bachelor of Science and Master of Arts degrees. He was educated and prepared far beyond the requirements for the study of medicine at that period. He graduated from the Johns Hopkins School of Medicine at the age of twenty-five. He began his medical career at St. Joseph's Hospital in Baltimore where his misfortune to develop pulmonary tuberculosis became a blessing to the people of the State of Maryland. Taking the cure led him into his long and brilliant career in the control and treatment of pulmonary tuberculosis. He became superintendent of the Maryland State Tuberculosis Sanatorium at Sabillisville in 1908. In 1920 he took charge of the tuberculosis care in the whole State of Maryland and continued in control of the Maryland State Program until 1943 when he retired because of failing health. His achievements in the field of tuberculosis are well known. His comfort to patients is better known since he held himself as an example of the result of treatment since he was brought there on his back and not expected to survive.

Dr. Cullen was a member of all the important medical societies and at one time was president of the Maryland State Medical Society.

He was an indefatigable worker and gave unstintingly of his time and energy. He was always willing to help anyone who was sick or in

trouble regardless of his station in life, his race or creed. He showed great loyalty to friends, employees and patients and this endeared him to them for all time. The writer is proud to have been one of his friends who enjoyed the loyalty and help as countless others did in so many different ways.

Dr. Cullen was an ardent sports fan and was particularly fond of baseball and football. He thoroughly enjoyed a good movie, especially the western or outdoor types. He was fond of cards, especially the game of pitch. He was very democratic and enjoyed people of all walks of life. He was a grand character; modest, humble, and as honest as the day is long. He cherished his family and it can truly be said that his goodness and greatness began at home. His wife, Ethel, and his daughter, Jeanne Margaret, were always an inspiration to him.

After his retirement Dr. Cullen remained vigorous and active. Death came swiftly as he had always hoped it would when his turn came. His death brought grief and sorrow to countless patients and friends.

Otto C. Brantigan, M.D., Governor for Maryland.

SIDNEY VALENTINE SEWELL

1880 - 1949

The death of Sir Sidney Valentine Sewell, F.C.C.P., Regent of the American College of Chest Physicians for Australia, on March 13, 1949, cast a gloom over the community and he will be mourned by hundreds of patients whom he had served so tirelessly for more than forty years.

His education began at the Caulfield Grammar School, which was followed by two years as a teacher in general subjects at the Hamilton College in the Western District of Victoria. On the eve of his twenty-first birthday he entered the University of Melbourne and went into residence at Queen's College. Sir Sidney gained first-class honors in medicine, surgery and obstetrics, and won the Beany Scholarship in Surgery. This splendid success entitled him to become senior resident medical officer at the Melbourne Hospital for twelve months, 1906-1907, and at the end of that time he was appointed acting medical superintendent during the absence of Dr. Amess through illness. Following this he lectured for several months in pathology at the Medical School in the place of Professor Sir Harry Allen, who was on sick leave.

He married Alice Maud, sister of Joseph Cuning, Senior Surgeon to the Royal Free Hospital, London, on March 18, 1908. In 1911 during the absence of Professor W. A. Osborne in North America and Europe, Dr. Sewell was selected to give the lectures on the central nervous system to the third year medical students which he did with great success.

He next became interested in the early diagnosis and care of pulmonary tuberculosis and joined the staff of the private sanatorium "Glenelg" at Balwyn. He traveled to England and saw the new treatment at Brompton Hospital by lung compression and he was one of the first to practice the method in Victoria.

In 1924 he went to the United States of America to visit and work in numerous clinics including those at Rochester (Mayo), Boston and New York, and accumulated much information concerning the control of tuberculosis for the Government of Victoria. For over a decade Dr. Sewell had waged a crusade against the scourge of tuberculosis and was

fearless in attacks on politicians for their neglect of such an important plan and on the medical profession for its apathy. Sir Sidney was the second president of the Royal Australasian College of Physicians, 1940-42.

In June 1945, he was created a Knight Bachelor for his distinguished work in medicine. The Council of the Royal College of Physicians conferred upon him in 1939 the honorary diploma of F.R.C.P., and the present government in Victoria will show its appreciation by naming one of the large eight-story buildings of the new Tuberculosis Sanatorium at Watsonia the "Sir Sidney Sewell Pathological Wing."

It was during Dr. Sewell's visit to the United States of America, upon the occasion of the 14th Annual Meeting of the American College of Chest Physicians, of which he was a member of the Board of Regents, that he was forced to return to his home as a result of a serious lung condition.

To his wife Lady Sewell, his two sons (Dr. Arnold Sewell and Bill, fourth year medical student) and his five daughters, the American College of Chest Physicians extends their sincerest sympathy.

OCTAVIO DE FREITAS

1871 - 1949

Dr. Octavio de Freitas was born in Teresina, Piaui, Brazil on February 24, 1871 and died in Recife, Pernambuco, Brazil on January 26, 1949. Dr. de Freitas received his degree of Doctor of Medicine at the Faculty of Medicine of Rio de Janeiro, Brazil. In his lifetime, Dr. de Freitas contributed much to medical literature. He was a founder of the Medical Faculty of Recife, an Emeritus Professor at the University of Recife, and has served as President of the Medical Society of Pernambuco, the Society of Phthisiology and the Society of History of Medicine. Dr. de Freitas was particularly interested in diseases of the chest and tuberculosis. He initiated the practice of BCG vaccination in the state of Pernambuco and was founder of a private organization named the "League Against Tuberculosis," serving as its President until his death. He was President of the Medical Congress of Pernambuco in 1909 and 1915. Dr. Octavio de Freitas was an indefatigable worker and with his death the community and the medical profession suffered a severe loss.

Joaquim S. Cavalcanti, M.D.,
Governor for the Northeast Brazilian Chapter.
